PRODUCT MONOGRAPH

Pr JAYDESS®

Levonorgestrel-releasing intrauterine system (13.5 mg)

Progestogen

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1: Product Information Summary

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
Intra-uterine	Intrauterine system / 13.5 mg levonorgestrel (LNG)	Barium sulphate, iron oxide, polydimethylsiloxane, polyethylene, silica, silver *For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

INDICATIONS AND CLINICAL USE

JAYDESS (levonorgestrel-releasing intrauterine system [13.5 mg]) is indicated for conception control for up to 3 years.

Geriatrics

JAYDESS is not indicated for use in postmenopausal women.

Pediatrics (< 18 years of age)

Safety and efficacy has been studied in women aged 18 and over. JAYDESS is not indicated for use before menarche.

CONTRAINDICATIONS

JAYDESS (levonorgestrel-releasing intrauterine system [13.5 mg]) is contraindicated in patients with the following conditions:

- known or suspected pregnancy
- current or recurrent pelvic inflammatory disease or conditions associated with increased risk for pelvic infections
- postpartum endometritis or septic abortion during the previous three months
- abnormal uterine bleeding of unknown etiology
- uterine anomalies including fibroids if they distort the uterine cavity

- uterine or cervical malignancy
- known or suspected progestogen-dependent neoplasia, including breast cancer
- cervicitis or vaginitis, including bacterial vaginosis or other lower genital tract infections until infection is controlled
- cervical dysplasia
- active liver disease or dysfunction
- actual benign or malignant liver tumours
- hypersensitivity to levonorgestrel or any of the other ingredients in the formulation or component of the container components of JAYDESS. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- a previously inserted intrauterine device (IUD) that has not been removed
- recent trophoblastic disease while hCG levels are elevated
- bacterial endocarditis

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Hormonal contraceptives **DO NOT PROTECT** against Sexually Transmitted Infections (STIs) including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms **IN COMBINATION WITH JAYDESS.**
- Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. Women should be counseled not to smoke (see **Cardiovascular** section below).
- **Uterine Perforation may occur with the use of intrauterine contraceptives including JAYDESS (see Uterine Perforation section).**

Carcinogenesis and Mutagenesis

Breast Cancer

Increasing age, inherited mutations, and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include nulliparity, first full-term pregnancy after the age of 30, menarche before the age of 12, never breastfed a child, and daily alcohol consumption. In some women, the use of hormonal contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. More thorough studies are needed to determine the definitive link between hormonal contraceptive use and the potential risk of breast cancer.

Breast self-examination should be discussed with women receiving hormonal contraceptives. Women should be instructed to notify their physicians whenever any masses are detected.

Spontaneous reports of breast cancer have been received during post-marketing experience with another levonorgestrel-releasing intrauterine system (LNG-releasing IUS). Two observational studies did not support a causal relationship between breast cancer and the other LNG-releasing IUS, however an elevated breast cancer risk cannot be totally excluded since these studies did not control for confounding factors such as use of oral hormonal contraception by control subjects, genetics and lifestyle and environmental factors such as smoking and alcohol.

There is currently no conclusive evidence of an association between JAYDESS use and development of breast cancer or progression of subclinical breast cancer.

Cardiovascular

An individual benefit-risk assessment in relation to continued use of JAYDESS should be carried out in the event of arterial thrombosis. In particular, removal of JAYDESS should be considered if severe arterial disease such as stroke or myocardial infarction occurs. In addition, JAYDESS should be used with caution in patients with a previous history of severe arterial disease such as stroke or myocardial infarction. Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence. There have been post-market reports of cardiovascular events, including myocardial infarction and stroke in women using another LNG IUS, although a causal relationship could not be clearly established in these cases.

Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Hormonal contraceptives increase this risk, especially with increasing age.

Other women who are independently at high risk for cardiovascular disease include those with diabetes, hypertension, abnormal lipid profile, or a family history of these risk factors.

Hypertension

If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during JAYDESS use, JAYDESS removal should be considered.

Congenital or Valvular Heart Disease

JAYDESS should be used with caution in women with congenital or valvular heart disease who are at risk of infective endocarditis. Antibiotic prophylaxis should be administered to such patients when inserting or removing JAYDESS.

Endocrine and Metabolism

Glucose Tolerance

Combination and progestogen-only oral contraceptives, including those containing levonorgestrel, may affect glucose tolerance in some users. Diabetic patients, and those with a family history of diabetes, should be observed closely to detect any alterations in carbohydrate

metabolism. Young diabetic patients whose disease is of recent origin, well controlled and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be closely observed. One published clinical study indicated no change in mean daily insulin requirements in women with Type 1 diabetes using another levonorgestrel (LNG)-releasing intrauterine system (IUS) over a 12-month period. (1)

Genitourinary

Bleeding Irregularities

Because irregular menstrual bleeding or spotting is common during the first few months of use, endometrial pathology should be excluded prior to insertion of JAYDESS. Irregular bleeding patterns in users of JAYDESS could mask the signs and symptoms of cervical or endometrial cancer. If bleeding irregularities develop after prolonged use, appropriate diagnostic measures should be undertaken.

Patients should be appropriately counseled on the likelihood of changes in menstrual patterns. Prolonged menstrual bleeding may occur during the first few months, however with continued use, bleeding patterns vary from regular scanty menstruation in some women to infrequent bleeding or amenorrhea in others. Infrequent bleeding (1 or 2 bleeding or spotting episodes per 90-day reference period) or amenorrhea develops gradually in 22.3% and 11.6% of users, respectively, by the end of the third year of use (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics**). Reduced bleeding increases the level of blood hemoglobin.

The possibility of pregnancy should be considered if menstruation does not occur after six weeks or more of amenorrhea, following a pattern of regular menses. A repeat pregnancy test is not necessary in amenorrheic women unless indicated by other symptoms.

Hematologic

An individual benefit-risk assessment in relation to continued use of JAYDESS should be carried out in the event of thrombosis. In particular, removal of JAYDESS should be considered if venous thromboembolic disease such as deep vein thrombosis or pulmonary embolism occurs. Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence. There have been postmarketing reports of arterial and venous thromboembolism (ATE, VTE) in women using another LNG-releasing IUS, although a causal relationship could not be clearly established in such cases. Epidemiological studies have indicated that women using progestogen-only oral contraceptives may have a slightly increased risk of venous thromboembolism; however, the results are not statistically significant. (2-4)

Appropriate diagnostic and therapeutic measures should be undertaken immediately if there are symptoms or signs of thrombosis in users of JAYDESS. Symptoms of thromboembolism include: unilateral leg pain and/or swelling, sudden severe pain in the chest whether or not it radiates to the left arm, sudden breathlessness, sudden onset of coughing, any unusual severe prolonged headache, sudden partial or complete loss of vision, diplopia, slurred speech or aphasia, vertigo, collapse with or without focal seizure, weakness or very marked numbness suddenly affecting one side or part of the body, motor disturbances and acute abdomen.

Symptoms or signs of retinal thrombosis are: unexplained partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions.

Other Risk Factors for Venous Thromboembolism
Other generalized risk factors for venous thromboembolism include but are not limited to a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index ≥30 kg/m^2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking. The risk of VTE may be temporarily increased with prolonged immobilization, major surgery, or trauma. Also patients with varicose veins and leg cast should be closely monitored.

Hepatic/Biliary/Pancreatic

Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of hormonal contraceptive use until markers of liver function return to normal (see **CONTRAINDICATIONS**).

To date, no studies have examined whether the avoidance of the first-pass effect through the liver, as with non-oral hormonal contraceptives, lessens concerns in women with liver conditions. (5)

Jaundice

Patients who have had jaundice should be given hormonal contraceptives only with great care and under close observation. If jaundice develops in a patient using JAYDESS, consideration should be given to removing the system. Hormonal contraceptive-related cholestasis has been described in women with a history of pregnancy-related cholestasis. This condition may recur with subsequent hormonal contraceptive use (See **CONTRAINDICATIONS**).

Neurologic

Headache

JAYDESS should be used with caution in women with a history of severe headache or migraine headache, including migraine with focal neurological symptoms (ie, asymmetrical visual loss or other symptoms indicating transient cerebral ischemia). The onset or exacerbation of migraine or the development of headaches with a new pattern that is recurrent, persistent or severe requires evaluation of the cause and consideration to remove JAYDESS (see **Cardiovascular** section).

Ophthalmologic

Contact Lenses

Any eye problems or discomfort occurring during use of a hormonal contraceptive, including those relating to the use of contact lenses, should be assessed. If this occurs, an ophthalmologist should be consulted. Temporary or permanent cessation of wear may be advised.

Peri-operative Considerations

Thromboembolic Complications – Post surgery

Women using JAYDESS who require surgery associated with prolonged immobilization should be followed closely for signs and symptoms of thromboembolism.

Psychiatric

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while using JAYDESS. In cases of a serious recurrence, consideration should be given to removing JAYDESS, since the depression may be drug-related.

Sexual Function/Reproduction

Ectopic Pregnancy

Women with a previous history of ectopic pregnancy, tubal surgery, or pelvic infection carry a higher risk of ectopic pregnancy. Carefully consider the possibility of an ectopic pregnancy in women who become pregnant while having JAYDESS in place. Pregnancies with JAYDESS use are rare, however, if a woman becomes pregnant with JAYDESS in situ, the relative likelihood of ectopic pregnancy is increased. Up to half of the pregnancies that occur with JAYDESS in place are ectopic. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain, especially in association with missed periods, or if an amenorrheic woman starts bleeding.

Women who choose JAYDESS should be told about the risk of ectopic pregnancy, including the possibility of impaired fertility or loss of fertility. Educate women to recognize and report to their physician any signs and symptoms of ectopic pregnancy.

In clinical trials, the overall incidence of ectopic pregnancy with JAYDESS is approximately 0.11 per 100 women-years. Women with a history of ectopic pregnancies were excluded from clinical trials with JAYDESS.

Expulsion

In clinical trials with JAYDESS, the incidence of expulsion was 3.2% (54 of 1665 subjects over 3 years) and in the same range as that reported for other IUDs and IUSs. Symptoms of the partial or complete expulsion of JAYDESS may include bleeding or pain. However, partial or complete expulsion can occur without the woman noticing it, leading to decrease or loss of contraceptive protection. As JAYDESS typically decreases menstrual bleeding over time, an increase of menstrual bleeding may be indicative of an expulsion (See **DOSAGE AND ADMINISTRATION – Expulsion**).

Ovarian Cysts / Enlarged Ovarian Follicles

Since the contraceptive action of JAYDESS is due mainly to its local effect on the uterus, ovulatory cycles with follicular rupture usually occur in women of fertile age. Sometimes atresia

of the follicle is delayed and folliculogenesis may continue. These enlarged follicles cannot be distinguished clinically from ovarian cysts.

Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia. In most cases, the enlarged follicles resolve spontaneously over two to three months' observation. Should an enlarged follicle fail to resolve spontaneously, continued ultrasound monitoring and other diagnostic or therapeutic measures may be appropriate. Rarely, surgical intervention may be required.

In clinical trials, ovarian cysts were reported as adverse drug reactions in approximately 13.2 % of women using JAYDESS including ovarian cyst, hemorrhagic ovarian cyst and ruptured ovarian cyst. Most were assessed as non-serious and did not require study drug discontinuation. (see **ADVERSE REACTIONS – Clinical Trial Adverse Drug Reactions)**.

Pelvic Infection

Jaydess is contraindicated in women with current or recurrent pelvic inflammatory disease or conditions associated with increased risk for pelvic infections (see **CONTRAINDICATIONS**). Conditions associated with an increased risk of PID include established immunodeficiency and acute malignancies affecting blood or leukemias.

The inserter provided with JAYDESS helps protect the system from contamination with micro-organisms during insertion, thereby minimizing the risk of pelvic infection. The exposed product should be handled with aseptic precautions. (See **DOSAGE AND ADMINISTRATION – Insertion Instructions.**) Known risk factors for pelvic inflammatory disease (PID) include multiple sexual partners, sexually transmitted infections, prior history of PID, and young age. Less common causes of pelvic inflammatory disease include pelvic actinomycosis and pelvic tuberculosis, both of which are extremely rare. There is an increased risk of PID related to the insertion procedure during 20 days following the insertion of IUDs. Thereafter, the risk of PID during the use of IUDs or levonorgestrel-releasing intrauterine systems is small. Patients should be advised to report to their physicians promptly if they experience symptoms suggestive of PID. (6-8) PID may be asymptomatic but tubal damage and resulting fertility issues may still occur.

If recurrent endometritis or pelvic infections are experienced, or if an acute infection does not respond to treatment within a few days, JAYDESS must be removed.

Sepsis

There have been very rare post-market reports of Group A streptococcal sepsis (GAS) temporally associated with intrauterine contraceptive insertion. Because death from GAS is more likely if treatment is delayed, it is important to be aware of these rare but serious infections. Aseptic technique during insertion of JAYDESS is essential in order to minimize serious infections such as GAS.

Uterine Perforation

Partial perforation (uterine embedment) or complete perforation of the uterus wall or cervix may occur during insertion with intrauterine contraceptives, although the perforation may not be detected until later. Pregnancy may result from partial or complete perforation. If partial or complete perforation occurs, JAYDESS must be located and removed; surgery may be required. Partial perforation (uterine embedment) can result in difficult removal. Delayed detection of perforation may result in migration outside the uterine cavity, adhesions, peritonitis, intestinal perforation and obstruction, abscesses and erosion of adjacent viscera. The number of uterine perforations is linked to the experience of the person inserting the system. (9) During clinical trials, perforation occurred at a rate between 0.1 and 1 per 1000 insertions (see **ADVERSE REACTIONS – Clinical Trial Adverse Drug Reactions**). Clinical trials with JAYDESS excluded breast-feeding women.

In a large, prospective, comparative, non-interventional cohort study (1 year follow-up period) in users of another LNG-IUS[1] and copper IUDs (N = 61,448 women), the incidence of perforation was 1.3 (95% CI:1.1-1.6) per 1000 insertions in the entire study cohort; 1.4 (95% CI: 1.1-1.8) per 1000 insertions in the cohort of another LNG-IUS, and 1.1 (95% CI: 0.7 - 1.6) per 1000 insertions in the copper IUD cohort. Extending the observational period to 5 years in a subgroup of this study (N = 39,009 women using another LNG-IUS or copper IUD), the incidence of perforation detected at any time during the entire 5-year period was 2.0 (95% CI: 1.6 – 2.5) per 1000 insertions; 2.1 (95% CI: 1.6 – 2.8) and 1.6 (95% CI: 0.9 – 2.5) for another LNG-IUS and copper IUD, respectively.

The study showed that both breast-feeding at the time of insertion and insertion up to 36 weeks after giving birth were associated with an increased risk of perforation (see Table 2). These risk factors were confirmed in the subgroup followed up for 5 years. Both risk factors were independent of the type of IUD inserted.

Table 2: Incidence of perforation per 1000 insertions for the entire study cohort observed over 1 year, stratified by breastfeeding and time since delivery at insertion (parous women)

	Breastfeeding at time of insertion	**Not breastfeeding at time of insertion**
Insertion ≤ 36 weeks after delivery	5.6 (95% CI 3.9-7.9; n=6047 insertions)	1.7 (95% CI 0.8-3.1; n=5927 insertions)
Insertion > 36 weeks after delivery	1.6 (95% CI 0.0-9.1; n=608 insertions)	0.7 (95% CI 0.5-1.1; n=41910 insertions)

The risk of perforations may be increased in women with abnormal uterine anatomy or fixed retroverted uterus.

To reduce the possibility of perforation postpartum, JAYDESS insertion should be delayed a minimum of 6 weeks after delivery or until uterine involution is complete. If involution is delayed, consider waiting until 12 weeks postpartum. Inserting JAYDESS immediately after

[1] "Another LNG-IUS" refers to an LNG-IUS that is slightly larger than JAYDESS and contains more levonorgestrel.

first trimester abortion is not known to increase the risk of perforation, but insertion after second trimester abortion should be delayed until uterine involution is complete.

To reduce the possibility of perforation, it is important to follow the recommended insertion technique. (See **DOSAGE AND ADMINISTRATION – Insertion Instructions**)

Inform patients before the procedure about the risk of uterine perforation and educate them on possible signs of this complication, including, but not limited to, severe low abdominal pain, which may be associated with bleeding after the procedure, loss of threads, or change in thread length.

Uterine Embedment

Embedment of JAYDESS in the myometrium may occur. Embedment may decrease contraceptive effectiveness and result in pregnancy. An embedded JAYDESS must be removed. Embedment can result in difficult removal, and may require surgery.

Special Populations

Pregnant Women/Intrauterine Pregnancy

The use of JAYDESS during an existing or suspected pregnancy is contraindicated (see also **CONTRAINDICATIONS**). If pregnancy occurs with JAYDESS in place, JAYDESS should be removed since any intrauterine system left in place may increase the risk of abortion and preterm labour. Removal of JAYDESS or probing of the uterus may result in spontaneous abortion. In the event of an intrauterine pregnancy with JAYDESS in place, consider the following:

a) Risk of septic abortion

b) Continuation of pregnancy

If JAYDESS cannot be removed or the woman chooses not to have it removed, she should be warned that failure to remove JAYDESS increases the risk of miscarriage, sepsis, premature labor, and premature delivery. Ectopic pregnancy should be excluded. The woman should be followed closely and advised to report any abnormal symptoms, such as fever, chill, cramping, abdominal pain, bleeding, vaginal discharge, or leakage of fluid.

c) Long-term effects and congenital anomalies

When pregnancy continues with JAYDESS in place, long-term effects on the offspring are unknown. Congenital anomalies in live births have occurred infrequently with another LNG-releasing IUS. No clear trend towards specific anomalies has been observed. Because of the intrauterine administration of levonorgestrel and local exposure of the fetus to the hormone, the possibility of teratogenicity following exposure to JAYDESS cannot be completely excluded. Some observational data support a small increased risk of masculinization of the external genitalia of the female fetus following exposure to progestogens at doses greater than those currently used for oral contraception. Whether these data apply to JAYDESS is unknown.

Nursing Women

Hormonal contraceptives are not recommended as the contraceptive method of first choice in breast-feeding women. A published study indicated that during lactation in users of another LNG releasing IUS (52mg), 0.1% of the daily maternal dose of levonorgestrel could be transferred to the newborn via milk. (10) Although levonorgestrel may be found in the breast milk of women using LNG releasing IUS, there does not appear to be a detrimental effect on growth or development of breast-fed infants whose mothers started using the product after six weeks postpartum. Progestogen-only contraceptive methods do not appear to affect the quantity and quality of breast milk.

Geriatrics

JAYDESS is not indicated for use in postmenopausal women.

Pediatrics (< 18 years of age)

Safety and efficacy has been studied in women aged 18 and over. JAYDESS is not indicated for use before menarche.

Monitoring and Laboratory Tests

Magnetic Resonance Imaging (MRI)

Nonclinical testing has demonstrated that a patient can be scanned safely after placement of JAYDESS ("MR Conditional") under the following conditions:

- Static magnetic field of 3-Tesla or less
- Spatial gradient magnetic field of 36,000 Gauss/cm (T/m) or less
- Maximum whole body averaged specific absorption rate (SAR) of 4W/kg in the First Level Controlled mode for 15 minutes of continuous scanning

In nonclinical testing, JAYDESS produced a temperature rise of less than 1.8°C at a maximum whole body averaged specific absorption rate (SAR) of 2.9 W/kg, for 15 minutes of MR scanning at 3T using a transmit/receive body coil. A small amount of imaging artifact may occur if the area of interest is in the same area or relatively close to the position of JAYDESS.

Physical Examination and Follow-up

Before insertion, the woman must be informed of the efficacy, risks, and side effects of JAYDESS. As well, before JAYDESS is inserted, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities, and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active. Pregnancy and sexually transmitted diseases should be excluded, and genital infections have to be successfully treated.

Women should be re-examined 4 to 12 weeks after insertion and at least once a year thereafter, or more frequently if clinically indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Task Force on Preventive Health Care.

See also **DOSAGE AND ADMINISTRATION – Medical Examination/Consultation.**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The majority of women experience changes in menstrual bleeding pattern after insertion of JAYDESS (levonorgestrel-releasing intrauterine system [13.5 mg]). Over time, the frequency of amenorrhea and infrequent bleeding increases, and the frequency of both prolonged and frequent bleeding decreases (see **WARNINGS AND PRECAUTIONS – Genitourinary**, ***Bleeding Irregularities***; and **ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics**).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse drug reactions (ADRs) were collected from a total of 1672 patients in contraception studies, including 1383 exposed for one year and 993 who completed the three year study. The data cover more than 40,000 cycles of exposure or more than 3800 women-years. ADRs were more common during the first year after insertion of JAYDESS, and then gradually decreased over time.

Table 3: Adverse drug reactions, phase II and III clinical trials, N = 1672 (3820.65 women-years)

System Organ Class (MedDRA)	Very common (≥ 10%)	Common (≥ 1% to < 10%)	Uncommon (≥ 0.1% to < 1%)	Rare (≥ 0.01% to < 0.1%)	Very rare (≥ 0.001% to < 0.01%)
Psychiatric disorders		Depressed mood/ Depression			
Nervous system disorders	Headache	Migraine			
Gastrointestinal disorders	Abdominal/ pelvic pain	Nausea			
Skin and subcutaneous tissue disorders	Acne/ Seborrhoea	Alopecia	Hirsutism		
Reproductive system and breast disorders	Bleeding changes including increased and decreased menstrual bleeding, spotting, oligomenorrhoea and amenorrhoea Ovarian cyst[a] Vulvovaginitis	Upper genital tract infection Dysmenorrhea Breast pain/ discomfort Device expulsion (complete and partial) Genital discharge	Uterine perforation[b]		

a Ovarian cysts had to be reported as ADRs if they were abnormal, non-functional cysts and/or had a diameter > 3 cm on ultrasound examination

b This frequency is based on a large, prospective, comparative, non-interventional cohort study. Please see **Postmarket Adverse Drug Reactions**. In clinical trials with JAYDESS that excluded breastfeeding women, the frequency of perforation was "rare".

Of the subjects treated with JAYDESS, 21.6% discontinued due to an adverse event. The rate of discontinuations due to adverse events decreased over time. The most common adverse reactions leading to discontinuation of JAYDESS were vaginal hemorrhage (3.3 %), device expulsion (3.2%), acne (2.7 %), pelvic pain (1.7 %), and abdominal pain (1.4 %), dysmenorrhea (1.3%) and abdominal pain lower (1.1%).

Postmarket Adverse Drug Reactions

In a large, prospective, comparative, non-interventional cohort study (1 year follow-up period) in users of another LNG-IUS and copper IUDs (N = 61,448 women), the incidence of perforation was 1.3 (95% CI:1.1-1.6) per 1000 insertions in the entire study cohort; 1.4 (95% CI: 1.1-1.8) per 1000 insertions in the cohort of another LNG-IUS, and 1.1 (95% CI: 0.7 - 1.6) per 1000 insertions in the copper IUD cohort. This study showed that breastfeeding at the time of insertion and insertion up to 36 weeks after giving birth are independent risk factors for perforation (see **WARNINGS AND PRECAUTIONS – Sexual Function/Reproduction, Uterine Perforation**).

DRUG INTERACTIONS

Drug-Drug Interactions

No drug-drug interaction studies have been conducted with JAYDESS.

The effect of hormonal contraceptives may be impaired by drugs which induce liver enzymes, specifically cytochrome P450 enzymes. The influence of these drugs on the efficacy of JAYDESS (levonorgestrel-releasing intrauterine system [13.5 mg]) has not been studied, but it is not believed to be of major importance due to the local action of JAYDESS.

Substances increasing the clearance of levonorgestrel

Substances which may increase the clearance of levonorgestrel include phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, and products containing St. John's wort.

Substances with variable effects on the clearance of levonorgestrel

When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestin.

Substances decreasing the clearance of levonorgestrel (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (eg, fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (eg, clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestin.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Tissue Specimens

Pathologists should be advised of JAYDESS therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination.

Drug-Lifestyle Interactions

The effect of JAYDESS on the ability to drive or to use machines has not been studied. Patients should be advised not to drive or use machines until they know how they react to JAYDESS.

DOSAGE AND ADMINISTRATION

Recommended Dose

Following insertion into the uterine cavity, JAYDESS (levonorgestrel-releasing intrauterine system [13.5 mg]) is effective for up to three years.

The *in vivo* release curve is characterized by an initial steep decline that slows down progressively resulting in little change after 1 year until the end of the intended 3-year period of use. Estimated *in vivo* delivery rates for different time points are provided in Table 4.

Table 4: Estimated *in vivo* release rates based on observed *ex vivo* residual content data

Time	Estimated *in vivo* release rate [micrograms/24 hours]
24 days after insertion	14
60 days after insertion	10
1 year after insertion	6
3 years after insertion	5
Average over 3 years	**6**

Administration

Medical Examination/Consultation

Before insertion, the patient must be informed of the efficacy, risks and side effects of JAYDESS. A thorough history and physical examination should also be performed prior to insertion, including a blood pressure determination. Breasts, liver, extremities, and pelvic organs should be examined. Cervical smear (Papanicolaou smear) should be performed as needed, according to healthcare professional's evaluation. Pregnancy and sexually transmitted diseases should be excluded and any genital infections must be successfully treated. The position of the uterus and the size of the uterine cavity should be determined. Fundal positioning of JAYDESS is particularly important in order to ensure uniform exposure of the endometrium to the progestogen, prevent expulsion and maximize efficacy. The instructions for insertion should be followed carefully. The patient should be re-examined 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.

Insertion, Removal and Replacement

JAYDESS should be inserted within seven days of the onset of menstruation. JAYDESS may be replaced by a new system at any time during the cycle. The system can also be inserted immediately after first trimester abortion. Postpartum insertions should be postponed until the uterus is fully involuted, and not earlier than six weeks after delivery. If involution is substantially delayed, consider waiting until 12 weeks postpartum. In case of a difficult insertion and/or exceptional pain or bleeding during or after insertion, the possibility of perforation should be considered and appropriate steps should be taken, such as physical examination and ultrasound.

JAYDESS is not suitable for use as a postcoital contraceptive.

Because irregular bleeding is common during the first months of therapy, it is recommended to exclude endometrial pathology before insertion of JAYDESS. If bleeding irregularities develop during prolonged treatment, appropriate diagnostic measures should be undertaken.

JAYDESS can be removed by gently pulling on the removal threads with forceps. If the threads are not visible and the system is in the uterine cavity, it may be removed using forceps. This may require dilatation of the cervical canal or other surgical intervention, such as hysteroscopy.

After removal of JAYDESS, verify that the system is intact. The system should be removed after three years of use. If the patient wishes to continue using JAYDESS, a new system can be inserted at the time of removal of the old one. If pregnancy is not desired, removal should be carried out during menstruation in women of fertile age provided that there appears to be a menstrual cycle. If the system is removed at some other time or the woman does not experience regular menses and the woman has had intercourse within a week, she is at risk of pregnancy unless a new system is inserted immediately following removal.

Insertion and removal may be associated with some pain and bleeding. The procedure may cause a fainting spell or precipitate a seizure in an epileptic patient. It is recommended to wait 24 to 48 hours before having sexual intercourse in the event of general discomfort after insertion of JAYDESS.

Expulsion

Symptoms of the partial or complete expulsion of JAYDESS may include bleeding or pain; however, a system may be expelled from the uterine cavity without the patient noticing it. Partial expulsion may decrease the effectiveness of JAYDESS. Since JAYDESS decreases menstrual flow, an increase in menstrual flow may indicate an expulsion. A displaced system should be removed. A new system can be inserted at that time and the patient should be advised on how to check for the presence of the system by feeling for the removal threads.

In clinical trials with JAYDESS, the incidence of expulsion was 3.2% (54 of 1665 subjects over 3 years), and in the same range as that reported for other IUDs and IUSs. Overall more expulsions occurred during the first 12 months after insertion.

In clinical trials with JAYDESS, more expulsions occurred in parous women, especially those with a history of vaginal births, than in nulliparous women.

Lost Removal Threads

If the threads are not visible upon follow-up examination, they may have retracted into the uterus or broken, or JAYDESS may have broken, perforated the uterus, or been expelled. If the length of the threads has changed from the length at the time of insertion, the system may have become displaced (see **DOSAGE AND ADMINISTRATION – Administration, *Expulsion***). Pregnancy must be excluded and the location of JAYDESS must be verified by sonography (JAYDESS contains a silver ring to facilitate detection by ultrasound), X-ray (JAYDESS is radiopaque), or by gentle exploration of the uterine cavity with a probe. If JAYDESS is displaced, remove it. A new JAYDESS may be inserted at that time or during the next menses if it is certain that conception has not occurred.

Insertion Instructions

Because the insertion technique is different from other intrauterine devices, it is important that physicians receive training on the correct insertion technique.

Physicians should become thoroughly familiar with the insertion instructions in their entirety before insertion of JAYDESS.

JAYDESS is supplied in a sterile package which should not be opened until required for insertion. It is sterilized with ethylene oxide. Do not resterilize. For single use only. Do not use if the seal of the sterile package is broken, or if the package is damaged or opened. The exposed product should be handled with aseptic precautions. Insert before the date indicated on the label.

JAYDESS is to be inserted into the uterine cavity within seven days of the onset of menstruation. JAYDESS can be replaced by a new system at any time in the cycle.

Preparation for Insertion

1. Visualize the cervix with the aid of a speculum and thoroughly cleanse the cervix and vagina with a suitable antiseptic solution.
2. Grasp the upper lip of the cervix with a tenaculum or suitable holding forceps to stabilize the uterus. If the uterus is retroverted, it may be more appropriate to grasp the lower lip of the cervix. Gentle traction on the holding forceps can be applied to straighten the cervical canal. The forceps should remain in position and gentle traction on the cervix should be maintained throughout the insertion procedure.
3. Gently advance a uterine sound through the cervical canal to the fundus to determine the depth and confirm the direction of the uterine cavity, and to exclude any evidence of intrauterine abnormalities (eg, uterine septum, synechiae or submucosal fibroids) or a previously inserted intrauterine contraceptive which has not been removed. If difficulty is encountered, consider dilatation of the canal. If cervical dilatation is required, consider using analgesics and/or paracervical block.

Insertion

Step 1–Opening of the sterile package

- First, open the sterile package completely (Figure 1). Then use aseptic technique and sterile gloves.

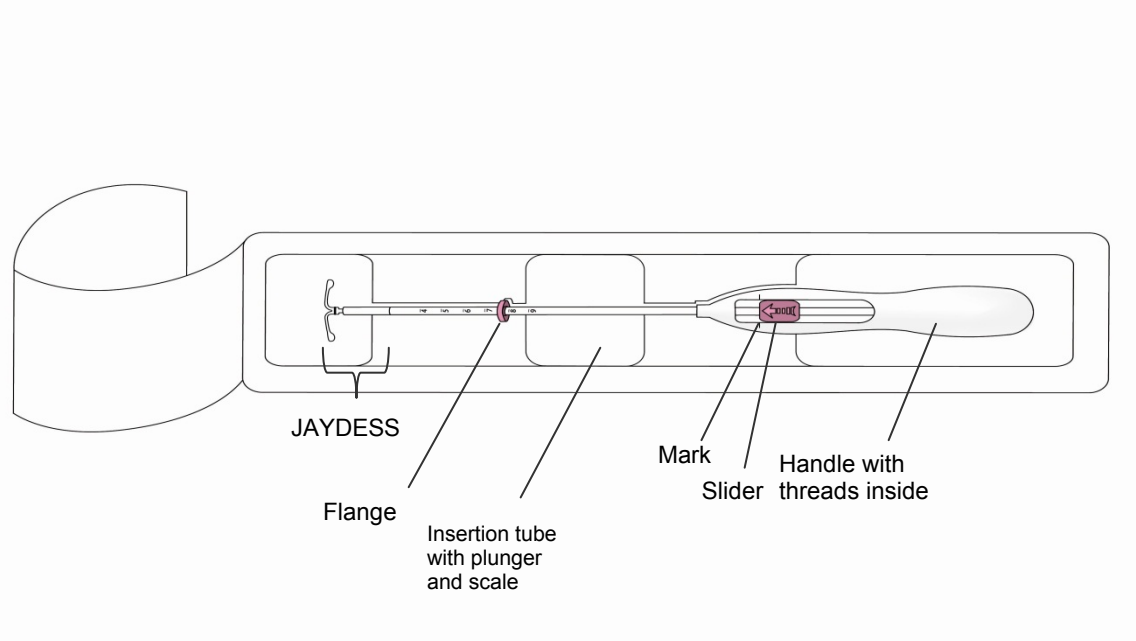


Figure 1: Sterile Package Containing JAYDESS

Step 2–Load JAYDESS into the insertion tube

- To load JAYDESS into the insertion tube, push the slider **forward** in the direction of the arrow to the furthest position (Figure 2).
- IMPORTANT! Do not pull the slider downwards as this may prematurely release JAYDESS. **Once released, JAYDESS cannot be re-loaded.**

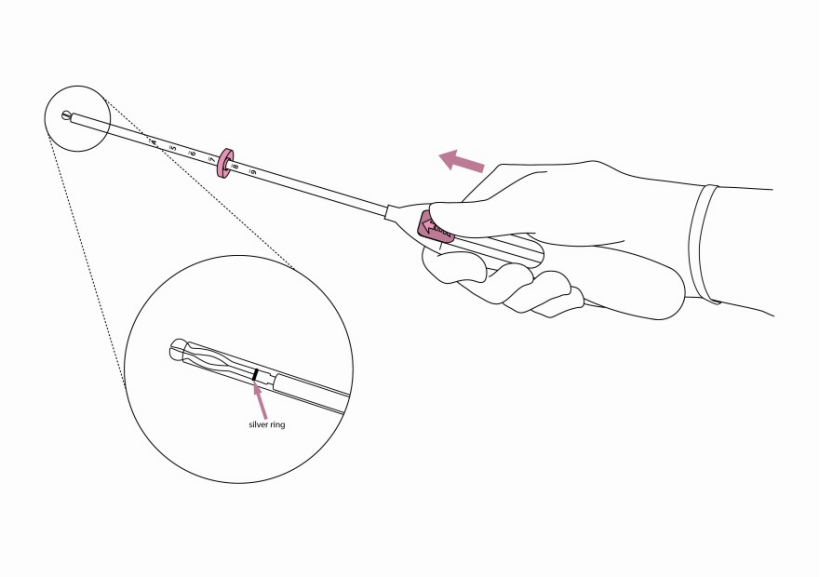


Figure 2: Loading JAYDESS into the Insertion Tube

Step 3–Setting the flange

- Holding the slider in the furthest position, set the **upper** edge of the flange to correspond to the sound measurement of the uterine depth (Figure 3).

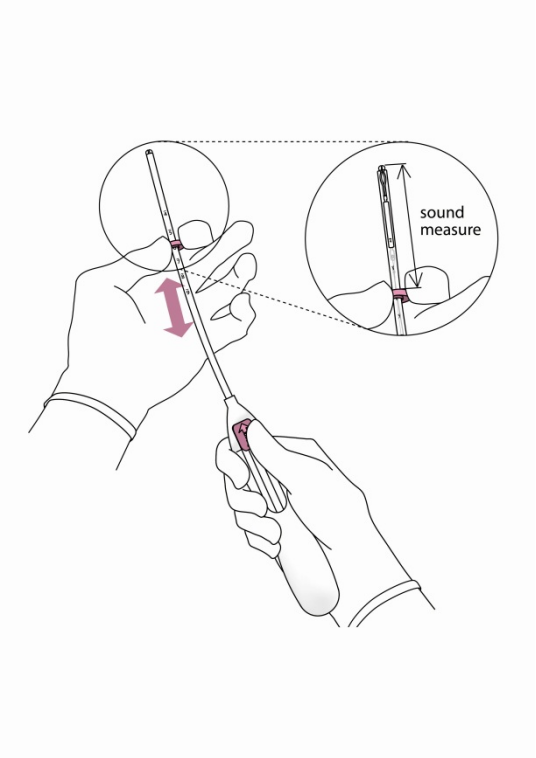


Figure 3: Setting the Flange to the Uterine Depth

Step 4–Advance the inserter through the cervix

- While holding the slider in the **furthest** position, gently advance the inserter through the cervical canal and into the uterine cavity **until the flange is approximately 1.5 to 2.0 cm from the external cervical os** (Figure 4).
- **NOTE: Do not advance flange to the cervix at this step.** Maintaining the flange 1.5 to 2 cm from the cervical os allows sufficient space for the arms to open (when released) within the uterine cavity.
- **IMPORTANT! Do not force the inserter. If necessary, dilate the cervical canal.**

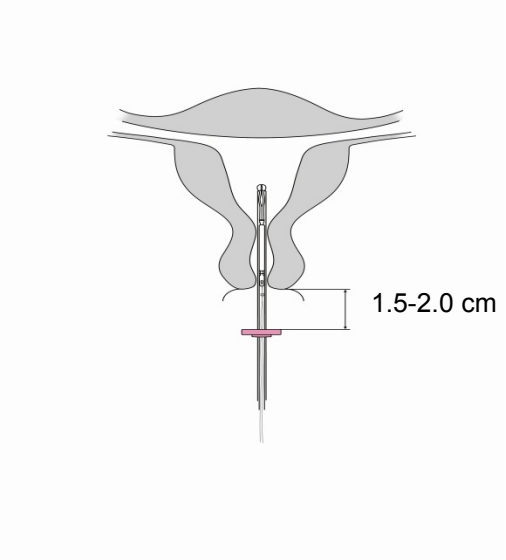


Figure 4: Advancing the Inserter Until Flange is 1.5 to 2 cm From Cervical Os

Step 5–Release the arms

- While holding the inserter steady, **pull the slider to the mark** to open the horizontal arms of JAYDESS (Figure 5). Wait approximately 10 seconds for the horizontal arms of JAYDESS to open completely.

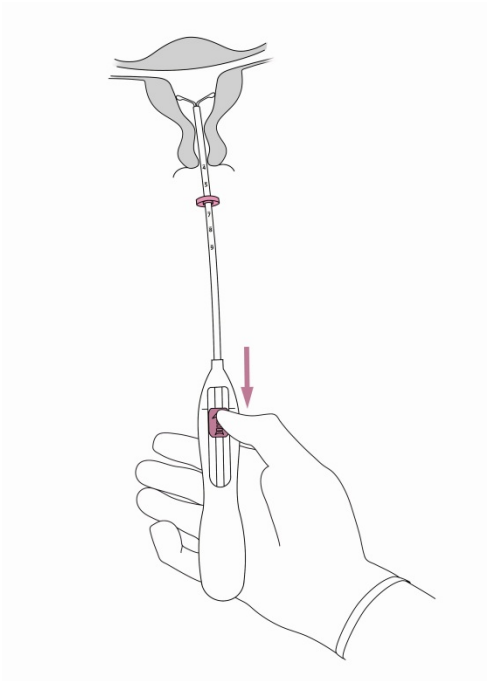


Figure 5: Releasing the Arms of JAYDESS

Step 6–Advance to fundal position

- Advance the inserter gently towards the fundus of the uterus **until the flange touches the cervix** or you feel fundal resistance. JAYDESS should now be in the desired fundal position (Figure 6).

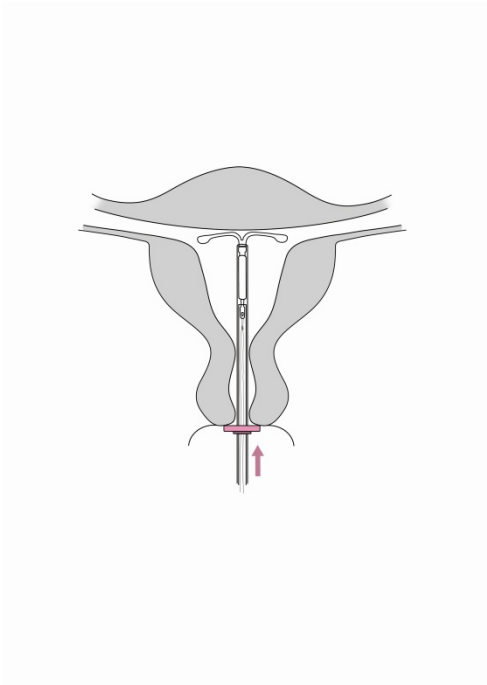


Figure 6: JAYDESS in the Fundal Position

Step 7–Release JAYDESS and withdraw the inserter

- While holding the inserter in place, **pull the slider all the way down** to release JAYDESS from the insertion tube (Figure 7). The threads will release automatically from the internal thread lock of the inserter.
- Gently remove the inserter by pulling it out.
- **Cut the threads perpendicular** to the thread length, for example, with sterile curved scissors, leaving about 2-3 cm visible outside of the cervix. NOTE: Cutting the threads at an angle may leave sharp ends.

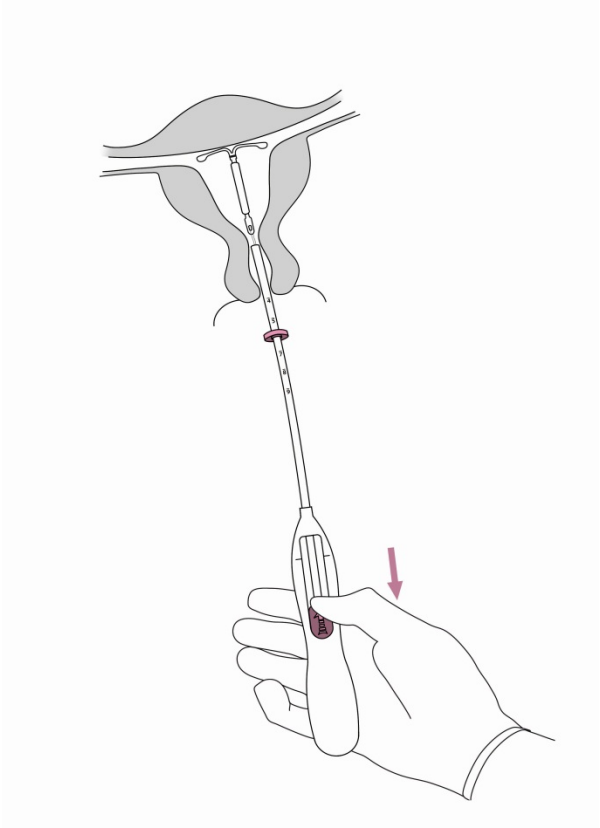


Figure 7: Releasing JAYDESS from the Insertion Tube

JAYDESS insertion is now complete.

In case difficulties arise during insertion, the patient complains of pain, or if there is any doubt that the system is not in the correct position, verify with ultrasound or X-ray. Remove the system if it is not positioned properly in the intrauterine cavity, and insert a new one. A removed system must never be reinserted.

Patients should be re-examined 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.

Use of Sanitary Pads

The use of sanitary pads is recommended. If tampons are used, they should be changed carefully to avoid inadvertently pulling the JAYDESS removal threads.

Removal/Replacement of JAYDESS

JAYDESS is removed by pulling on the threads with a pair of forceps (Figure 8).

A JAYDESS system should not remain in the uterus longer than 3 years.

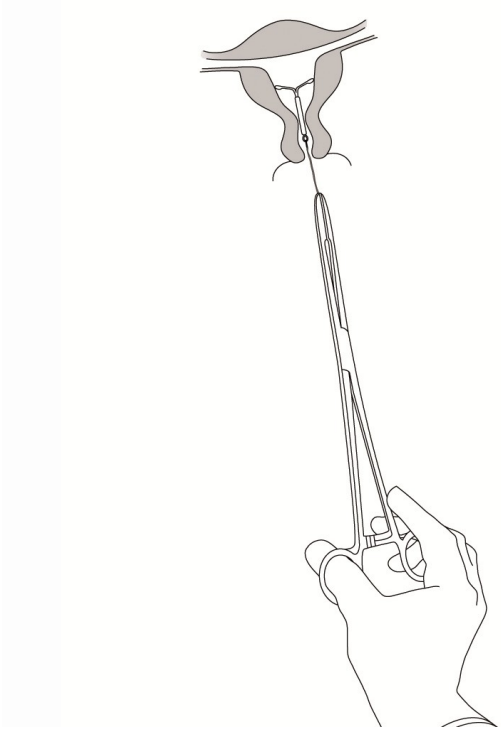


Figure 8: Removal of JAYDESS

Missed Dose

JAYDESS should be removed after 3 years. If the user wishes to continue using JAYDESS, a new system can be inserted to replace the old system. If the system has been used for a longer period of time than 3 years, pregnancy should be ruled out before insertion of a new system.

OVERDOSAGE

Not applicable. JAYDESS is an intrauterine system.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

JAYDESS (levonorgestrel-releasing intrauterine system [13.5 mg]) consists of a small polyethylene T-shaped frame with a cylindrical reservoir containing levonorgestrel around the vertical stem of the T frame (see Figure 9). In addition, the vertical stem contains a silver ring to aid in detection by sonography located close to the horizontal arms. 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.

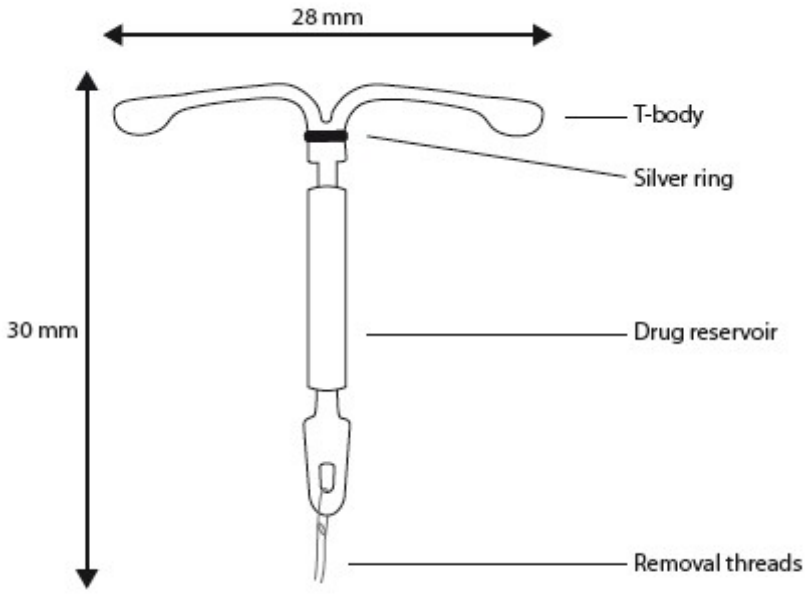


Figure 9: JAYDESS (levonorgestrel-releasing intrauterine system [13.5 mg])

JAYDESS is a long acting reversible contraceptive (LARC). After insertion in the uterus, JAYDESS releases levonorgestrel continuously for up to 3 years. Intrauterine administration allows a very low daily dosage, as the hormone is released directly to the target organ. JAYDESS contains a total of 13.5 mg of levonorgestrel; the *in vivo* release curve is characterized by an initial steep decline that slows down progressively resulting in little change after 1 year until the end of the intended 3-year period of use. Estimated *in vivo* delivery rates for different time points are provided in Table 4. JAYDESS does not contain any estrogen.

Pharmacodynamics

JAYDESS has mainly local progestogenic effects in the uterine cavity. The high levonorgestrel concentration in the endometrium down-regulates endometrial estrogen and progesterone receptors. The endometrium becomes relatively insensitive to the circulating estradiol and a strong antiproliferative effect is seen. Morphological changes of the endometrium and a weak local foreign body reaction were observed during use. Thickening of the cervical mucus prevents passage of the sperm through the cervical canal. The local milieu of the uterus and of the fallopian tubes inhibits sperm mobility and function, preventing fertilization.

The use of JAYDESS does not alter the course of future fertility; upon removal of JAYDESS, women return to their normal fertility. In a study in which 3 different doses of LNG-IUSs were investigated, 6 out of 7 women in the JAYDESS group (85.7%) wishing to become pregnant conceived within 12 months after removal of the system.

The duration and volume of menstrual bleeding and menstrual blood loss gradually decreases after the first several months of use, after an initial increase in the number and irregularity of bleeding and spotting days. With continued use, bleeding patterns vary from regular menstruation in some women, to irregular or prolonged bleeding in other women, and amenorrhea in others. In most women, there is a trend over time towards less frequent and shorter episodes of bleeding.

Menstrual bleeding patterns were recorded by all women throughout their participation in clinical trials with JAYDESS, starting from the day of insertion. Menstrual bleeding patterns were assessed using the World Health Organization 90-day reference period method. (11) Data reported for each reference period reflect the number of women actually enrolled in trials during that specific reference period and for whom valid bleeding diaries were returned. The following bleeding patterns were observed:

- During the first 90 days, less than 1% of women experienced amenorrhea, 8% infrequent bleeding, 31% frequent bleeding, 42% irregular bleeding, and 59% prolonged bleeding.
- During the second 90 days, 3% of women experienced amenorrhea, 19% infrequent bleeding, 12% frequent bleeding, 28% irregular bleeding, and 17% prolonged bleeding.
- At the end of year 1, 6% of women experienced amenorrhea, 20% infrequent bleeding, 8% frequent bleeding, 23% irregular bleeding, and 9% prolonged bleeding.
- At the end of year 3, 12% of women experienced amenorrhea, 22% infrequent bleeding, 4% frequent bleeding and 3% prolonged bleeding. The end of year 3 result for irregular bleeding in particular is artificially inflated (46%) because removal was not timed to coincide with a complete 90-day reference period. The result from the preceding 90-day reference period (17%) provides a more relevant indication of the observed incidence of irregular bleeding near the end of the 3-year period.

Amenorrhea is defined as no bleeding or spotting throughout the 90 day reference period. Infrequent bleeding is the occurrence of 1 or 2 bleeding/spotting episodes per 90 day reference period. Frequent bleeding is the occurrence of more than 5 bleeding/spotting episodes per 90 day reference period. Prolonged bleeding is the occurrence of bleeding/spotting episodes lasting more than 14 days per 90 day reference period. Irregular bleeding is the occurrence of 3 to 5 bleeding/spotting episodes and less than 3 bleeding/spotting-free intervals of 14 days or more per 90 day reference period.

In the phase III study, the mean number of bleeding/spotting days in the first 30 days was 18.0 and decreased to 5.7 by one year (see Figure 10).

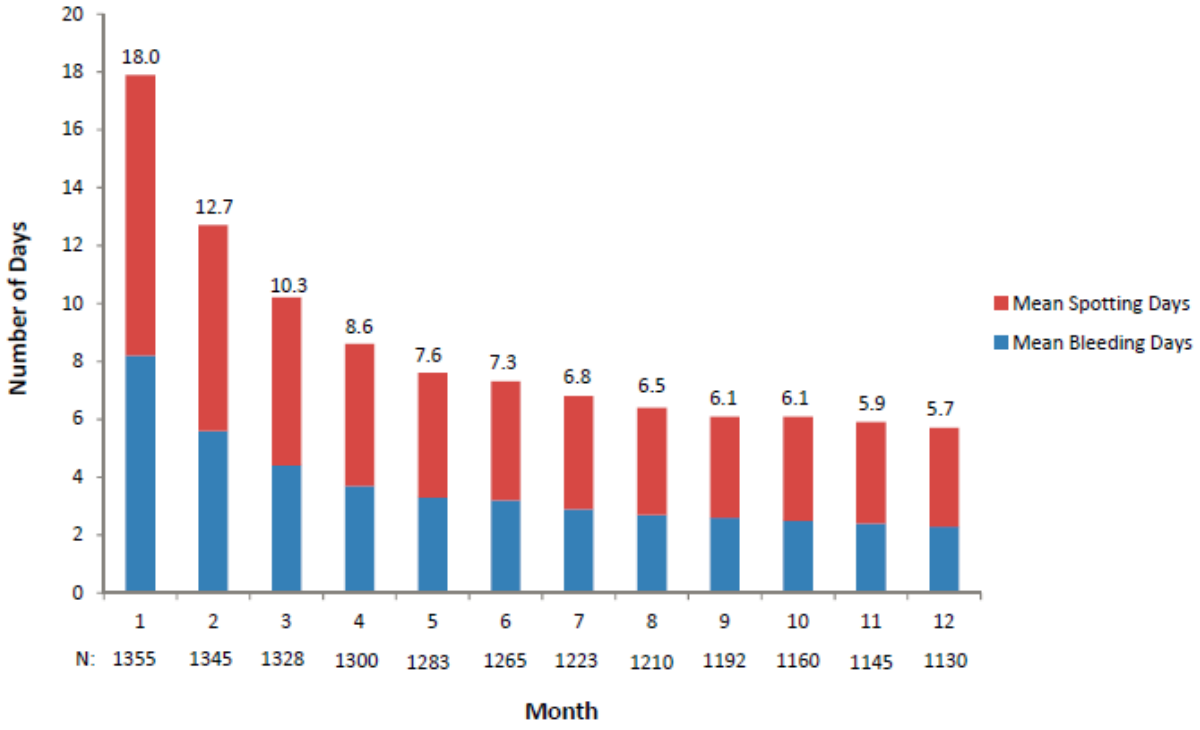


Figure 10: Mean number of bleeding/spotting days by 30-day reference periods in the phase III trial

The altered menstrual bleeding pattern that occurs with JAYDESS use is a result of the direct action of levonorgestrel on the endometrium and is not due to the suppression of the ovulatory cycle. There is no clear difference in follicle development, ovulation, or estradiol and progesterone production in women with different bleeding patterns. Ovarian function is normal and estradiol levels are maintained even when users of JAYDESS are amenorrheic. Ovulation was observed in all women throughout the phase II study, and in most women in the phase III study. Specifically, evidence of ovulation was seen in 34 out of 35 women in the first year, in 26 out of 27 women in the second year, and in all 26 women in the third year in the two studies combined. (12, 13)

Endometrial histology has been investigated in clinical studies examining the intrauterine release of levonorgestrel at rates ranging from approximately 5 (average release rate at the end of 3 years for JAYDESS) to 20 µg/day after insertion. During treatment, a strong progestogenic effect was observed in the majority of cases. The decrease in number of bleeding days and amount of menstrual bleeding seen during the clinical studies reflects the high degree of endometrial suppression.

In the phase III pivotal study, cervical histology was evaluated at screening and annually. Epithelial cell abnormalities were seen in 2.2% of women at screening, and the maximum was observed at Month 24 with 6.5% of women. At the final visit 3.8% of women had epithelial cell abnormalities detected.

Pharmacokinetics

Absorption

Following insertion, levonorgestrel is immediately released from the IUS into the uterine cavity. Maximum serum concentrations of levonorgestrel are reached within the first two weeks after insertion of JAYDESS. In a subset of 7 subjects, maximum observed serum LNG concentration was 192 ± 105 pg/mL, reached after 2 days (median) of JAYDESS insertion. Seven days after insertion, a mean levonorgestrel concentration of 162 pg/mL was determined. Thereafter, serum concentrations of levonorgestrel decline over time to reach mean concentrations of 59 pg/mL after 3 years.

Distribution

Levonorgestrel is bound non-specifically to serum albumin and specifically to sex hormone-binding globulin (SHBG). Less than 2 % of the circulating levonorgestrel is present as free steroid. Levonorgestrel binds with high affinity to SHBG. Total serum concentration of levonorgestrel increases or decreases in proportion to the concentration of SHBG. Within one month after insertion of JAYDESS, the concentration of SHBG declines by about 30 %. Afterwards, plateau-like SHBG concentrations are observed with a tendency to increase towards baseline values over time. The mean apparent volume of distribution of levonorgestrel is about 106 L.

Metabolism

Levonorgestrel is extensively metabolized. The most important metabolic pathways are the reduction of the Δ4-3-oxo group and hydroxylations at positions 2α, 1β and 16β, followed by conjugation. CYP3A4 is the main enzyme involved in the oxidative metabolism of levonorgestrel. The available *in vitro* data suggest that CYP mediated biotransformation reactions may be of minor relevance for levonorgestrel compared to reduction and conjugation.

Excretion

The total clearance of levonorgestrel from plasma is approximately 1.0 mL/min/kg. Only trace amounts of levonorgestrel are excreted in unchanged form. The metabolites are excreted in feces and urine at an excretion ratio of about 1. The excretion half-life is about 1 day.

Special Populations and Conditions

Geriatrics (> 65 years of age)

JAYDESS is not indicated for use in postmenopausal women.

Pediatrics (< 18 years of age)

Safety and efficacy has been studied in women aged 18 and over. JAYDESS is not indicated for use before menarche.

Hepatic Insufficiency

JAYDESS has not been studied in women with hepatic impairment. JAYDESS is contraindicated in women with acute liver disease or liver tumour (see **CONTRAINDICATIONS** section).

Renal Insufficiency

JAYDESS has not been studied in women with renal impairment.

STORAGE AND STABILITY

Store JAYDESS (levonorgestrel-releasing intrauterine system [13.5 mg]) at room temperature (between 15°C and 30°C).

Keep out of reach of children and pets.

SPECIAL HANDLING INSTRUCTIONS

JAYDESS (levonorgestrel-releasing intrauterine system [13.5 mg]) should be handled with aseptic precautions. Used JAYDESS systems should be considered biohazardous waste and disposed of accordingly. Care should be taken to ensure the remaining hormonal ingredients are not introduced into water/sewer systems.

DOSAGE FORMS, COMPOSITION AND PACKAGING

JAYDESS (levonorgestrel-releasing intrauterine system [13.5 mg]) contains 13.5 mg of levonorgestrel in a cylindrical-shaped reservoir composed of a whitish or pale yellow matrix of levonorgestrel and polydimethylsiloxane covered with a semiopaque membrane made of polydimethylsiloxane and silica (see Figure 9). The reservoir is mounted on the vertical stem of a polyethylene T-body. The vertical stem contains a silver ring to facilitate detection by sonography which is located close to the horizontal arms. The T-body is pigmented with barium sulphate and has a loop at one end of the vertical stem and two horizontal arms at the other end. The polyethylene removal threads attached to the loop of the T-body are pigmented with iron oxide. The vertical stem of the IUS is loaded in the insertion tube at the tip of the inserter. The IUS and inserter are essentially free of visible impurities.

JAYDESS is in a sterile package within an inserter. The EvoInserter (Figure 11), which is used for insertion of JAYDESS into the uterine cavity, consists of a symmetric two-sided body and slider that are integrated with flange, lock, insertion tube and plunger. The outer diameter of the insertion tube is 3.8 mm. The vertical stem of JAYDESS is loaded in the insertion tube at the tip of the inserter. The arms are pre-aligned in the horizontal position. The removal threads are contained within the insertion tube and handle. Once JAYDESS has been placed, the inserter is discarded.

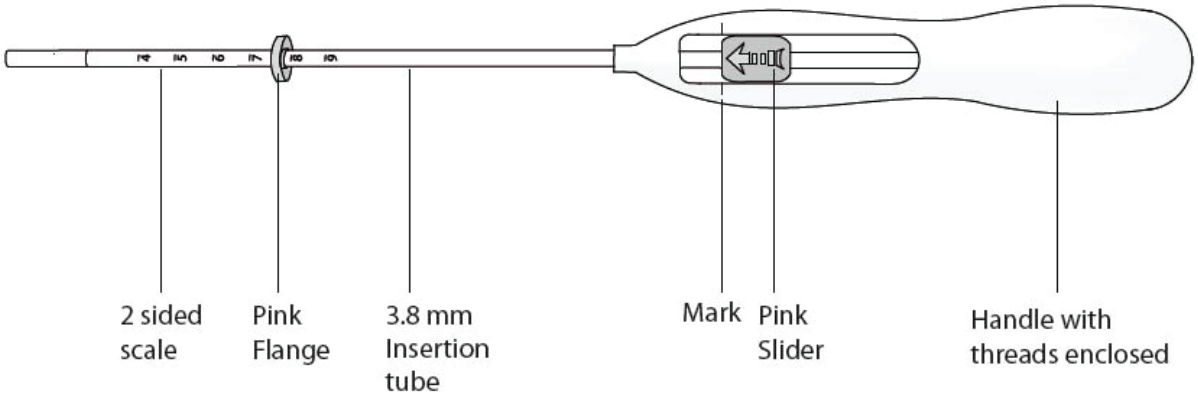


Figure 11: JAYDESS EvoInserter

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

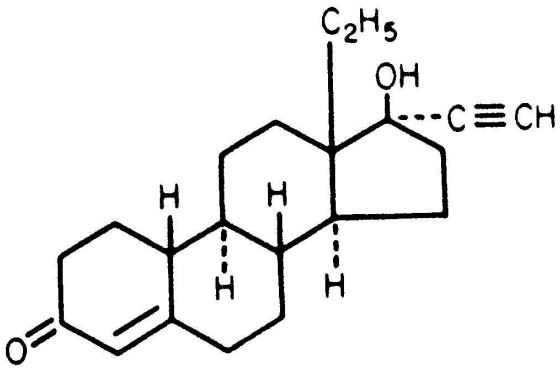
Proper name: levonorgestrel

Chemical name: 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-,(17α)(-)

Molecular formula: $C_{21}H_{28}O_2$

Molecular weight: 312.45

Structural formula:



Physicochemical properties: Levonorgestrel is a white to off-white crystalline powder, practically insoluble in water and slightly soluble in ethanol, in vegetable oils, in chloroform, in ether and in alkaline solutions. The melting range is between 232°C and 239°C.

CLINICAL TRIALS

The contraceptive efficacy of JAYDESS (levonorgestrel-releasing intrauterine system [13.5 mg]) has been evaluated in a multi-centre (Europe, North America, and South America), open-label, randomized clinical study with 1432 women aged 18-35 including 38.8 % (556) nulliparous women of whom 83.6% (465) were nulligravid using JAYDESS. Approximately 40% of women in this study were 25 years or younger. Approximately 80% of women enrolled in the study were Caucasian, 11% Hispanic, 5% Black and 1% of Asian origin. The mean body mass index was 25.3 kg/m^2 (range 15.6 – 54.9 kg/m^2).

The 1-year Pearl Index was 0.41 (95% CIs: 0.13 – 0.96) and the 3-years Pearl Index was 0.33 (95% CIs: 0.16 – 0.6). The failure rate was approximately 0.4% at 1 year and the cumulative failure rate was approximately 0.9% at 3 years. The failure rate also includes pregnancies due to undetected expulsions and perforations. Since the use of JAYDESS does not require daily intake

compliance by the users, the pregnancy rates in typical use are similar to those observed in controlled clinical trials.

The first insertion attempt was successful in 1380/1432 women (96.4 %); the second attempt was successful in 46/49 (93.9 %) women. Study investigators assessed the insertion procedure as easy in 1283/1432 women (89.6 %). There was a trend towards the insertion procedure being more difficult in nulliparous women and those who have only had Caesarean-section deliveries.

Most women experienced no pain (20.6%, 295/1432) or only mild pain (43.9 %, 629/1432) during insertion of the IUS. A total of 390 (27.2 %) experienced moderate pain and 118 (8.2%) experienced severe pain. There was a trend towards less pain in parous women compared to nulliparous women.

In the pivotal study A52238, almost 60% of the women completed the planned treatment duration of 3 years with LCS12. The majority of premature discontinuations were due to adverse events (319/613). The frequency of discontinuations due to progestogen-related side effects or any bleeding problems/abnormalities (including amenorrhea) were 3.4% and 4.7%, respectively. Other reasons for discontinuation included a desire to become pregnant, no further need for contraception, and withdrawal of consent. (13)

General Information

The following table gives typical pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant within the first year of use.

Table 5: Reported Pregnancies per 100 Women Within the First Year of Use

Hormonal Intrauterine system (IUS)	less than 1
Copper Intrauterine device (IUD)	less than 1
Progesterone Injection	6
Combined hormonal contraceptive (pill, patch or ring)	9
Diaphragm	12
Male condom	18
Female condom	21
Sponge, spermicide	12-28
Withdrawal method	22
Natural family planning	24
No method	85

DETAILED PHARMACOLOGY

Human Pharmacology

See Part I: **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics**.

Pharmacodynamics

Levonorgestrel (LNG) is a 19-nortestosterone derivative with potent progestogenic effects, but no significant estrogenic activity.

In rabbits, evidence of transformation of the endometrium was observed after subcutaneous administration of 0.01 mg LNG corresponding to 2 μg/kg/day. Transformative effects are also histologically recognizable in the rabbit endometrium when LNG is administered orally in doses ranging from 0.03 to 0.3 mg per animal corresponding to approximately 6 to 60 μg/kg/day.

In pregnant rats, ovariectomized within the first 4 days after conception, the subcutaneous administration of 0.002 mg LNG had a blastocyst-maintaining effect. The antiestrogenic or progestogenic activity of levonorgestrel has also been demonstrated in various test models in rats and mice. The potency of LNG is significantly higher than progesterone and about 83 times stronger than chlormadinone acetate.

LNG does not have any significant estrogenic activity and androgenic effects are only detectable after large doses. LNG also influences the gonadotrophic function of the anterior lobe of the pituitary gland in all experimental tests.

Like other progestogens, relative large doses of LNG lead to increases in insulin secretion in rats and dogs.

TOXICOLOGY

Levonorgestrel (LNG) is widely used in gynaecology in various ways: either in combination as the progestin component in oral contraceptives, and in hormonal replacement therapy or alone for contraception in minipills, subdermal implants and intrauterine systems. The toxicological profile of LNG after systemic and local administration is well known and the available evidence indicates that this hormone is a safe drug in the above-mentioned indications.

Acute Toxicity

Single dose toxicity studies with LNG in rats and mice using the oral, intraperitoneal and subcutaneous route of application indicate a low acute toxicity with lethal doses in the g/kg body weight range.

Long-term Toxicity

Systemic tolerance studies were performed in mice, rats, dogs and monkeys either with LNG or the racemate d,l-norgestrel. Systemic tolerance findings were as expected and in line with findings that have been described in these species after prolonged treatment with other progestins. Most findings could directly be related to the progestogenic activity of LNG on target organs or on the endocrine regulation. Furthermore, clinical and laboratory findings observed in one or more species, such as increased body weight gains, alterations in serum lipid (cholesterol or triglyceride) levels, increases in plasma fibrinogen, increases in blood sedimentation rate and the decreases in red blood cell parameters are also well known effects of repeated dosages of progestogens, including progesterone in the affected species.

The effect of LNG on the induction of mammary hyperplasia (acinar and/or ductal) in dogs is considered a species-specific effect. No compound-related alterations were observed in tumourigenicity studies with LNG in mice, rats and monkeys. In dogs, long-term oral treatment with the highest daily dose of 0.5 mg/kg LNG led to an increased incidence in benign mammary tumours. This is a well known effect of progestogens in dogs, the mechanism of which is assumed to be due to stimulation of growth hormone secretion that exerts a mammotrophic effect in this species. Endocrine regulation and the sensitivity of the mammary gland to progestogens and growth hormone are known to be unique for the dog, and have no predictive value for human risk assessment. Thus, taking into consideration biocompatibility and the absence of genotoxicity of the LNG-IUS and its components, the absence of proliferative or neoplastic changes in the local and systemic tolerance studies in rats and monkeys, and the extensive clinical experience with LNG and with another levonorgestrel (LNG)-releasing intrauterine system (IUS) (52 mg), JAYDESS is regarded to possess no carcinogenic potential.

Reproductive Toxicology

An early developmental formulation of JAYDESS was studied in rabbits following intrauterine administration. The absence of compound-related maternal toxicity, embryotoxicity, teratogenicity or effects on fetal development in pregnant rabbits suggests that JAYDESS is not a reproductive toxicant.

Reproduction toxicity tests were performed with LNG or norgestrel, for evaluation of effects on fertility and peri-/postnatal toxicity in rats and on embryotoxicity in mice, rats and rabbits. No adverse effects are to be expected at clinically relevant dose levels.

Mutagenicity

Mutagenicity tests were performed with LNG to detect gene mutations and chromosomal aberrations. Based on the results obtained from *in vitro* and *in vivo* tests, there is no evidence that LNG has a mutagenic potential. Furthermore, LNG has been tested into the potential to induce DNA-repair in rat hepatocytes in vitro (Unscheduled DNA Synthesis-test) and into its DNA-adduct forming potential in human liver slices *in vitro*. None of these tests gave an indication of a genotoxic potential of LNG.

Neither the LNG-IUS nor its components showed any evidence of a genotoxic potential *in vitro* or *in vivo*.

Biocompatibiliy studies

A wide range of biocompatibility tests were performed with the materials and components of JAYDESS. Many of the tests have been conducted during the development of another LNG-releasing IUS (52 mg), which mainly consists of the same materials as JAYDESS. Therefore, studies conducted with another LNG-releasing IUS (52 mg), or modified versions of it, are also relevant for JAYDESS. There was no evidence of any bioincompatibility including absence of a genotoxic potential of the components of JAYDESS. No systemic or local intolerance was detected in chronic studies in rats (intramuscular, subcutaneous) or Cynomolgus monkeys (intrauterine implantation). The endometrial effects of the modified intrauterine systems observed in monkey studies were similar to those seen in clinical studies.

It is unlikely that cytotoxic concentrations of silver ions can be achieved *in vivo* by the silver ring used in JAYDESS. Also, taking into consideration that there was no evidence of hemolytic potential or mutagenicity *in vitro* and no local or systemic intolerance *in vivo* after exposure to the silver ring for up to 39 weeks, there is no cause for concern for the use of the silver ring in JAYDESS for detection and differentiation by ultrasound.

Based on the results of the studies conducted with JAYDESS materials after ethylene oxide sterilization and considering guidance given by the ISO standard 10993, the limit of 2 ppm is considered to be toxicologically justified and not pose a risk to human health.

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PART III: CONSUMER INFORMATION

Pr JAYDESS®

Levonorgestrel-releasing intrauterine system

This leaflet is Part III of a three-part "Product Monograph" published when JAYDESS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about JAYDESS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

JAYDESS is used for the prevention of pregnancy (contraception) for up to 3 years.

What it does:

JAYDESS is an intrauterine system (IUS). Levonorgestrel is a hormone commonly used in combination oral contraceptives (the "Pill") and is similar to progesterone, a sex hormone produced naturally by the body. JAYDESS works by slowly releasing levonorgestrel into the uterus at a rate of approximately 14 µg per day after 24 days and is reduced to approximately 10 µg per day after 60 days. It then declines progressively to 5µg per day after three years. The mean dissolution rate of levonorgestrel is approximately 6 µg per day over the period of three years. This amount of levonorgestrel:

- reduces the normal monthly thickening of the lining of the uterus.
- thickens the cervical mucus which prevents passage of sperm through the cervical canal (opening to the uterus).

These effects of levonorgestrel prevent pregnancy.

JAYDESS contains a total of 13.5 mg of levonorgestrel, which is enough hormone to prevent pregnancy for up to 3 years.

JAYDESS does not contain any estrogen.

Clinical trials found that there was less than 1 pregnancy per year for every 100 women using JAYDESS.

Other Ways to Prevent Pregnancy

Other methods of birth control are available to you. When used properly, other methods of birth control are effective enough for many women.

The following table gives typical pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant within the first year of use.

Reported Pregnancies per 100 Women Within the First Year of Use

Hormonal Intrauterine system (IUS)	less than 1
Copper Intrauterine device (IUD)	less than 1
Progesterone Injection	6
Combined hormonal contraceptive (pill, patch or ring)	9
Diaphragm	12
Male condom	18
Female condom	21
Sponge, spermicide	12-28
Withdrawal method	22
Natural family planning	24
No birth control	85

The pregnancy rates listed in the table vary widely. This is because of differences in how carefully and regularly people use each method of birth control. Regular users may have lower pregnancy rates. Others may expect pregnancy rates in the middle ranges. This does not apply to IUDs because they are placed in the uterus and do not depend on user compliance.

When it should not be used:

JAYDESS is not suitable for every woman. In a small number of women, serious side effects may occur. Your doctor can advise you if you have any conditions that would pose a risk to you. The use of JAYDESS should always be supervised by your doctor. You should not use JAYDESS if you:

- have any allergies to the hormone levonorgestrel, or to any of the other ingredients of JAYDESS, or to components of the container (see the sections in this leaflet titled "What the medicinal ingredient is" and "What the nonmedicinal ingredients are")
- are pregnant or if you suspect you may be pregnant
- currently have pelvic inflammatory disease (PID) or have had recurrent PID (see the paragraph in this leaflet titled "Infections")
- have an infection of your lower genital tract, ie, vagina and/or cervix (neck of the womb), until the infection is controlled
- had an infection of the uterus (womb) after delivering a baby
- have bleeding from the vagina that has not been explained
- have a condition of the uterus that distorts the uterine cavity, such as large fibroids
- have cell abnormalities in the cervix (your doctor can tell you if you have this)
- have a known or suspected progestogen-dependent tumour, including breast cancer

- have liver disease or liver tumour
- have had an infection of the uterus (womb) after having an abortion during the past 3 months
- have cancer of the uterus or the cervix (uterine or cervical malignancy)
- have a previously inserted intrauterine device (IUD) that has not been removed
- have pregnancy related tumours
- have bacterial endocarditis (an infection of the heart valves or lining of the heart)

What the medicinal ingredient is:

levonorgestrel

What the nonmedicinal ingredients are:

Barium sulphate, iron oxide, polydimethylsiloxane, polyethylene, silica, silver

What dosage forms it comes in:

Each JAYDESS (levonorgestrel-releasing intrauterine system (13.5 mg)) is packaged with EvoInserter, an insertion device, and contains 13.5 mg of levonorgestrel to deliver up to 14 µg per day after 24 days and is reduced to approximately 10 µg per day after 60 days. It then declines progressively to 5µg per day after three years, with a mean rate of approximately 6 µg per day over 3 years.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Hormonal Contraceptives including JAYDESS DO NOT PROTECT against Sexually Transmitted Infections (STIs) including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms IN COMBINATION WITH JAYDESS.
- **Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. Women should be counseled not to smoke.**
- **JAYDESS may penetrate or perforate (punch a hole) in the wall of the uterus.**

BEFORE you use JAYDESS talk to your doctor or pharmacist if you have or have had any of the following conditions:

- are breast-feeding
- have given birth in the last 36 weeks
- have had a stroke, heart attack or any heart problems.
- have an abnormality of your heart or if you have any problem with your heart valves
- have a history of blood clots (thrombosis)
- have a history of migraine, dizziness or blurred vision
- have severe headaches
- have or have had jaundice (a yellowing of the skin, whites of the eyes and/or nails)
- are diabetic or have a family history of diabetes, have high blood pressure or abnormal blood lipid levels
- you smoke
- have a family history of blood clots, heart attacks, or strokes

If you see a different doctor, inform him/her that you are using JAYDESS. You should inform your doctor if you are scheduled for Magnetic Resonance Imaging (MRI), since JAYDESS can be safely scanned with MRI under most standard conditions.

Tell your doctor if you are scheduled for any laboratory tests, since certain tests may be affected by hormonal contraceptives. Also, tell your doctor if you are scheduled for surgery requiring prolonged bed rest.

JAYDESS should be used only under the supervision of a doctor, with regular follow-up to identify side effects associated with its use. Your visits may include a blood pressure check, a breast exam, an abdominal exam and a pelvic exam, including a Pap smear. Visit your doctor 4 to 12 weeks after the initial examination. Afterward, visit your doctor at least once a year. Use JAYDESS only on the advice of your doctor and carefully follow all directions given to you. Otherwise, you may become pregnant.

If you and your doctor decide that, for you, the benefits of JAYDESS outweigh the risks, you should be aware of the following:

The Risks of Using JAYDESS

1. Diabetes

In diabetic users of JAYDESS, the blood glucose concentration should be closely monitored.

2. Infections

There is an increased risk of a serious pelvic infection called pelvic inflammatory disease (PID) in the first three weeks after insertion of an intrauterine system or device. Other known risk factors include multiple sexual partners, frequent intercourse, and young age. PID can cause serious problems such as infertility, ectopic pregnancy, or constant pelvic pain. PID is usually treated with antibiotics; however, more serious cases of PID may require surgery. Tell your doctor right away if you have any of these signs of PID: long-lasting or heavy bleeding, unusual vaginal discharge, low abdominal (stomach area) pain, painful sex, chills or fever.

3. Ectopic Pregnancy

Ectopic pregnancy (development of a fertilized egg outside the uterus) is possible when using JAYDESS, as it is in women

using no contraception. However, if you accidentally become pregnant while using JAYDESS, an ectopic pregnancy is more likely. Ectopic pregnancy is a serious condition. Therefore, you should tell your doctor if you have lower abdominal pain, especially if you have missed a period and/or have unexpected bleeding, since these can be signs of an ectopic pregnancy.

4. Cysts on the Ovary

Cysts on the ovary commonly occur in women using JAYDESS. These cysts usually disappear on their own and within a few months. However, cysts can sometimes cause pain and may need medical attention.

5. Uterine Perforations

Most often during insertion, JAYDESS may penetrate or perforate (punch a hole in) the wall of the uterus, but this is uncommon. If this happens, JAYDESS must be removed.

The risk of perforation is higher in women who are breastfeeding at the time of JAYDESS insertion and/or when JAYDESS is inserted up to 36 weeks after delivery. The risk of perforation may be increased in women with an abnormally shaped uterus or with the uterus fixed and leaning backwards.

6. Use While Breast Feeding

Small quantities of levonorgestrel, the medicinal ingredient in JAYDESS, have been found in the milk of breast-feeding women using another LNG-releasing IUS. However, there does not appear to be a detrimental effect on growth or development of breast-fed infants whose mothers started using the product six weeks after delivery. Levonorgestrel does not appear to affect the amount or the quality of breast milk. You can use JAYDESS during breast-feeding.

7. Use in Pregnancy

If you become pregnant with JAYDESS in place, you should have it removed as soon as possible. If it is left in place during pregnancy, the chances of having a miscarriage or premature delivery increase. The effect of levonorgestrel on a developing infant is not well known, and therefore a detrimental effect cannot be completely ruled out. Removal of JAYDESS or probing of the uterus may result in spontaneous abortion. You should check with your doctor about risks to your unborn child.

8. Use After Pregnancy and Abortion

Following childbirth, JAYDESS should be inserted only after the womb has returned to its normal size, and not earlier than 6 weeks after delivery.

JAYDESS can be inserted immediately after a first trimester abortion.

9. Pregnancy After Stopping JAYDESS

If you wish to become pregnant, ask your doctor to remove JAYDESS. Your usual level of fertility should return soon after the system is removed. Approximately 86% of women wishing to become pregnant conceive within 12 months after removal of the system.

Driving or Using Machines

The effect of JAYDESS on the ability to drive or to use machines has not been studied. Do not drive or use machines until you know how you react to JAYDESS.

How Will JAYDESS Affect My Periods?

JAYDESS may affect your menstrual cycle. It can change your menstrual periods so that you have spotting (a small amount of bleeding), shorter or longer periods, lighter or heavier bleeding, or no bleeding at all.

Many women have frequent spotting or light bleeding in addition to their periods for the first 3-6 months after they have JAYDESS placed. Some women may have heavy or prolonged bleeding during this time. Please inform your healthcare professional, especially if this persists.

Overall, you are likely to have a gradual reduction in the amount and number of days of bleeding each month. Some women eventually find that periods stop altogether.

When JAYDESS is removed, periods soon return to normal.

What if I Stop Having Periods?

Over time, your menstrual period may gradually disappear when using JAYDESS. This is because of the effect of the hormone on the lining of the uterus. The normal monthly thickening of the uterine lining with blood does not happen; therefore, there is little or no bleeding, as happens during a usual menstrual period. It does not necessarily mean you have reached menopause or are pregnant.

If, however, you are having regular menstrual periods and then do not have one for 6 weeks or longer, it is possible that you may be pregnant. You should speak to your doctor.

INTERACTIONS WITH THIS MEDICATION

Please inform your doctor or pharmacist if you are taking or have recently taken any other drugs or herbal products, even those without a prescription.

Hormonal contraceptives may become less reliable if you are also taking drugs that affect the liver (such as primidone, barbiturates, phenytoin, carbamazepine, rifampicin, and griseofulvin) at the same time. The influence of these drugs on the reliability of JAYDESS has not been studied, but is unlikely since JAYDESS releases a very small amount of hormone and delivers the hormone inside the uterus.

The T-frame of JAYDESS contains barium sulphate, which makes it visible in X-ray examinations. JAYDESS also contains a small silver ring, which makes it visible during ultrasound examinations.

See also ABOUT THIS MEDICATION: When it should not be used, and SIDE EFFECTS AND WHAT TO DO ABOUT THEM.

PROPER USE OF THIS MEDICATION

Usual dose

What it looks like:

JAYDESS consists of a small, white, T-shaped frame made from soft, flexible plastic. The vertical and horizontal arms of the T are approximately 3 cm in length. The vertical arm is surrounded by a narrow, cylindrical shaped reservoir that contains levonorgestrel. Two fine plastic threads are attached to the tip of the vertical arm. These threads are intended to be used for removal of the system and also serve to check its presence once it is in place. In addition, the vertical stem contains a silver ring located close to the horizontal arms, which is visible under ultrasound examination.

How is JAYDESS Inserted?

Before JAYDESS is inserted, you will have a pelvic examination to determine the position and size of your uterus. Your doctor will insert the thin flexible plastic tube of the insertion device containing JAYDESS into your uterus. At this point you may feel a little discomfort.

Once JAYDESS is in the correct position, your doctor will withdraw the tube leaving the system in place in the uterus. Finally, your doctor will trim the removal threads to a suitable length.

After insertion you may feel some cramp-like menstrual pain; however, this usually disappears within a few days.

Most women find that the insertion procedure causes minor discomfort; however, for some it may be more uncomfortable. If concerned, you may wish to discuss the need for a painkiller or local anesthetic with your doctor. Some women may feel faint after JAYDESS is inserted, but this feeling subsides after a short rest. The insertion procedure may precipitate a seizure in epileptic patients.

It is uncommon, but part or all of JAYDESS may penetrate the wall of the uterus during insertion and come to rest outside the uterus. If this happens the system must be removed.

When Should JAYDESS be Inserted?

JAYDESS should be inserted within seven days of starting your period. When replacing an existing system for a new one, it is not necessary to wait for your period.

How Long Does Insertion Take?

The insertion procedure usually takes a few minutes after your doctor has completed the pelvic examination.

How Quickly Does JAYDESS Start to Work?

When JAYDESS is inserted within seven days of starting your period, you will be protected from pregnancy immediately However, it is best to wait 24 to 48 hours before having sexual intercourse in the event of general discomfort.

How Often Should I Have JAYDESS Checked?

You should have JAYDESS checked approximately 4 to 12 weeks after it is inserted, again at 12 months and then once a year until it is removed. JAYDESS can stay in place for 3 years before it must be removed.

How Can I Check if JAYDESS is in Place?

After each menstrual period or about once a month, you should check by feeling if the threads are still in place. Your doctor will show you how to do this. Do not pull on the threads as you may accidentally pull JAYDESS out.

If you cannot feel the threads, this may indicate that JAYDESS has fallen out or uterine perforation has occurred. See your doctor and in the meantime, use another method of nonhormonal contraception. You should also see your doctor if you can feel the lower end of JAYDESS itself.

Will JAYDESS Interfere With Sexual Intercourse?

During sexual intercourse, you or your partner should not be able to feel JAYDESS. If you can feel JAYDESS, or any pain or discomfort that you suspect may be caused by it, then you should not have sexual intercourse until you see your doctor to verify it is still in the correct position.

The removal threads may be felt by your partner during intercourse.

Can Tampons be Used?

Use of sanitary pads is recommended. If tampons are used, you should change them with care so as not to pull the threads of JAYDESS.

Can JAYDESS Fall Out?

It is unlikely, but possible that JAYDESS can come out either completely or partially. If this happens, you are not protected against pregnancy.

An unusual increase in the amount of bleeding during your period might be a sign that this has happened. If you think JAYDESS has come out, use another method of nonhormonal contraception until you see your doctor.

Removal of JAYDESS

JAYDESS should not be left in place for more than 3 years. You should see your doctor when you want to have JAYDESS taken out. Removal of JAYDESS is usually very easy. However, you should be aware that you may become pregnant upon removal of JAYDESS if you have had sexual intercourse during the previous week.

Tell your doctor if you have had sexual intercourse during the preceding week.

Missed Dose

If you wish to continue using JAYDESS after 3 years, your doctor can insert a new system after removing the old system. If the same JAYDESS system has been left in place for longer than 3 years, you may become pregnant. Pregnancy should be ruled out before insertion of a new system.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects with JAYDESS are more common during the first months after insertion; they gradually decrease over time.

Menstrual bleeding irregularities are the most common side effects of JAYDESS during the first months after the system is inserted, but these effects should decrease over time.

Very common side effects include: headache, abdominal/pelvic pain, acne/oily skin, bleeding changes including increased and decreased menstrual bleeding, spotting, oligomenorrhea (infrequent periods) and amenorrhea (absence of bleeding), ovarian cyst, vulvovaginitis (inflammation of the external genital organs or vagina).

Common side effects include: depressed mood/depression, migraine, nausea, alopecia (hair loss), upper genital tract infection, dysmenorrhea (painful menstruation), breast pain/discomfort, device explusion (complete and partial), genital discharge.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ Effect		Talk with your doctor or pharmacist	
		Only if severe	**In all cases**
Common	Vaginal bleeding	✓	
	Symptoms of vaginal infection, such as itching, or unusual or increased vaginal discharge		✓
	Headache	✓	
	Abdominal pain/ pelvic pain		✓
	Expulsion of JAYDESS		✓
	Migraine	✓	
Uncommon	Severe lower abdominal pain which may be together with bleeding, possibly meaning perforation of the uterus.		✓
	Persistent lower abdominal pain, together with fever or unusual discharge from the vagina, possibly meaning pelvic infection.		✓
	Persistent lower abdominal pain, together with nausea or breast tenderness and/or vaginal bleeding, possibly meaning intrauterine pregnancy, miscarriage, or ectopic pregnancy.		✓
	Dizziness		✓
	Skin rash, hives, eczema (itchy skin lesions)		✓

This is not a complete list of side effects. For any unexpected effects while taking JAYDESS, contact your doctor or pharmacist.

HOW TO STORE IT

Store JAYDESS at room temperature (between 15°C and 30°C).

Keep out of reach of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffectTM Canada Website at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

This document plus the full product monograph, prepared for health professionals can be found at http://www.bayer.ca or by contacting the manufacturer at the above mentioned phone number and email address.

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