DATA SHEET

1. JAYDESS® 13.5 mg intrauterine contraceptive device

Jaydess 13.5 mg intrauterine contraceptive device

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Jaydess is an intrauterine system (IUS) containing 13.5 mg levonorgestrel. For details of release rates, see Section 5.2.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Jaydess consists of a whitish or pale yellow core covered with a semi-opaque membrane, which is mounted on the vertical stem of a T-body. In addition, the vertical stem contains a silver ring located close to the horizontal arms. The white T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. Brown coloured removal threads are attached to the loop. 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception for up to 3 years.

4.2 Dose and method of administration

Jaydess is inserted into the uterine cavity and is effective for up to three years.

The *in vivo* release rate is approximately 14 µg/24 hours after 24 days and is reduced to approximately 10 µg/24 hours after 60 days. It then declines progressively to 6 µg/24 hours after one year and 5 µg/24 hours after three years. The average levonorgestrel *in vivo* release rate is approximately 8 µg/24 hours over the first year of use and 6 µg/24 hours over the period of three years.

Jaydess, when inserted according to the insertion instructions, has a failure rate of approximately 0.4% at 1 year and a cumulative failure rate of approximately 0.9% at 3 years. The failure rate also includes pregnancies due to undetected expulsions and uterine perforations.

Care must therefore be given to undertake adequate training in the correct insertion technique and ensure the availability of appropriate instruments for the insertion of Jaydess.

4.2.1 Medical examination/consultation

Before insertion, the woman must be informed of the efficacy, risks and side effects of Jaydess. A physical examination including pelvic examination and examination of the breasts should be conducted. Cervical smear should be performed as needed, according to Healthcare Professional's evaluation. Standard testing procedures should be used to exclude pregnancy

and STIs, and genital infections must have been successfully treated before insertion. The position of the uterus and the size of the uterine cavity must be determined. Fundal positioning of Jaydess is particularly important in order to ensure uniform exposure of the endometrium to the progestogen, prevent expulsion and maximise efficacy. Therefore, the instructions for insertion should be followed carefully. Insertion and removal may be associated with some pain and bleeding. The procedure may precipitate fainting as a vasovagal reaction, or a seizure in an epileptic patient. The woman should be re-examined 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.

Emphasis should be given to training in the correct insertion technique.

Irregular bleeding and spotting are common in the first months of therapy with all levonorgestrel-releasing intrauterine system (LNG-IUSs) including Jaydess. If bleeding becomes heavier and/or more irregular over time, appropriate diagnostic measures should be taken as irregular bleeding may be a symptom of endometrial polyps, hyperplasia or cancer.

4.2.2 Insertion and removal/replacement

It is recommended that Jaydess should only be inserted by physicians/healthcare professionals who are experienced in IUS insertions and/or have undergone training on the Jaydess insertion procedure.

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. Jaydess can also be inserted immediately after first trimester abortion.

Postpartum insertions should be postponed until the uterus is fully involuted, however 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 post-coital contraceptive.

Jaydess can be distinguished from other IUSs by the combination of the visibility of the silver ring on ultrasound and the brown colour of the removal threads. The T-frame of Jaydess contains barium sulfate which makes it visible in X-ray examination.

Jaydess is removed by gently pulling on the threads with forceps. If the threads are not visible and the system is found to be in the uterine cavity on ultrasound exam, it may be removed using narrow forceps. This may require dilatation of the cervical canal or surgical intervention.

The system should be removed no later than by the end of the third year. If the woman wishes to continue using the same method of contraception and no contraindications exist, a new system can be inserted immediately following removal of the original system.

If pregnancy is not desired, the removal should be carried out within seven days of the onset of menstruation, provided the woman is experiencing regular menses. If the system is removed at some other time during the cycle or the woman does not experience regular menses and the woman has had intercourse within a week, she is at risk of pregnancy. To ensure continuous contraception, a new system should be immediately inserted or an alternative contraceptive method should have been initiated. It is important to use another form of contraception in the week leading up to the removal of Jaydess.

After removal of Jaydess, the system should be examined to ensure that it is intact.

4.2.3 Special populations

4.2.3.1 Paediatric population

The safety profile of Jaydess observed in a study of 304 post-menarcheal adolescents was consistent with that in the adult population. Efficacy is expected to be the same for post-menarcheal adolescents under the age of 18 as for users 18 years and older. Use of this product before menarche is not indicated.

4.2.3.2 Elderly

There is no indication for the use of Jaydess in post-menopausal women.

4.2.3.3 Hepatic impairment

Jaydess has not been studied in women with hepatic impairment. Jaydess is contraindicated in women with acute liver disease or liver tumour (see Section 4.3).

4.2.3.4 Renal impairment

Jaydess has not been studied in women with renal impairment.

4.3 Contraindications

- Pregnancy
- Acute or recurrent pelvic inflammatory disease or conditions associated with increased risk for pelvic infections
- Lower genital tract infection
- Postpartum endometritis or infected abortion during the past three months
- Cervicitis
- Cervical intraepithelial neoplasia
- Uterine or cervical malignancy
- Confirmed or suspected hormone dependent tumours including breast cancer
- Abnormal uterine bleeding of unknown etiology
- Congenital or acquired uterine anomaly including fibroids which would interfere with insertion and/or retention of the intrauterine system (i.e. if they distort the uterine cavity)
- Acute liver disease or liver tumour
- Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings and precautions for use

Jaydess should be used with caution after specialist consultation, or removal of the system should be considered if any of the following conditions exist or arise for the first time:

- migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischaemia
- exceptionally severe headache
- jaundice

- marked increase in blood pressure
- severe arterial disease such as stroke or myocardial infarction
- acute venous thromboembolism

Data on use with Jaydess in nulliparous women is limited to approximately 36% of the study population.

4.4.1 Tumours

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COCs), mainly using estrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. As breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The risk of having breast cancer diagnosed in progestogen-only pill users is possibly of similar magnitude to that associated with COC. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs.

An individual benefit-risk assessment should be made in women in whom breast cancer is diagnosed while using Jaydess. Removal of Jaydess should be considered.

Irregular bleeding may be a symptom of underlying pathologies such as endometrial polyps, hyperplasia or cancer. Endometrial pathology should therefore be excluded before insertion of Jaydess (see also Section 4.2.1).

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV). Benign hepatic adenomas have been found to be associated with the use of oral contraceptives containing levonorgestrel. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage. The contribution of the progestin component of oral contraceptives to the development of hepatic adenomas is not known.

4.4.2 Heart disease

Jaydess should be used with caution in women who have congenital heart disease or valvular heart disease and who are at risk of infective endocarditis.

4.4.3 Diabetes

Low-dose levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of Jaydess. However, there is generally no need to alter the therapeutic regimen in Type I diabetics using LNG-IUS.

4.4.4 Infrequent bleeding/amenorrhoea

Infrequent bleeding and/or amenorrhea develops gradually in about 22.3 % and 11.6 % of users, respectively, by the end of the third year of use. Pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation. A repeated pregnancy test is not necessary in subjects who remain amenorrhoeic unless indicated by other signs of pregnancy.

4.4.5 Pelvic infection

While Jaydess and the inserter are supplied in a sterile pack, they may, due to bacterial contamination during insertion, become a vehicle for microbial transport in the upper genital tract. Pelvic infection has been reported during use of any IUS or IUD. In clinical trials, pelvic inflammatory disease was observed more frequently at the beginning of Jaydess use, which is consistent with published data for copper IUDs, where the highest rate of pelvic inflammatory disease occurs during the first 3 weeks after insertion and decreases thereafter.

Patients should be fully evaluated for risk factors associated with pelvic infection (e.g. multiple sexual partners, sexually transmitted infections (STIs), prior history of PID). Pelvic infections such as pelvic inflammatory disease may have serious consequences and it may impair fertility and increase the risk of ectopic pregnancy.

As with other gynaecological or surgical procedures, severe infection or sepsis (including group A *Streptococcal* sepsis) can occur following IUD insertion.

If a woman experiences recurrent endometritis or pelvic inflammatory disease or if an acute infection is severe or does not respond to treatment, Jaydess must be removed.

Bacteriological examinations are indicated and monitoring is recommended, even with discrete symptoms indicative of infections.

4.4.6 Expulsion

In clinical trials with Jaydess, the incidence of expulsion was low 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.

A partially expelled Jaydess should be removed. A new system can be inserted at that time provided pregnancy has been excluded and no other contraindications exist.

A woman should be advised how to check the threads of Jaydess and to contact her healthcare provider if the threads cannot be felt.

4.4.7 Perforation

Perforation or penetration of the uterine corpus or cervix by an intrauterine contraceptive may occur, most often during insertion, although it may not be detected until sometime later, and may decrease the effectiveness of Jaydess. Excessive pain or bleeding during insertion or while Jaydess is *in situ* may be indicative of a perforation. Such occurrences and/or lost threads should be further investigated. Should a perforation occur, the system must be removed as soon as possible; surgery may be required.

In a large, prospective, comparative, non-interventional cohort study in users of other IUDs (n=61,448 women) with a 1-year observational period, 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.

The study showed that both breastfeeding at the time of insertion and insertion up to 36 weeks after giving birth were associated with an increased risk of perforation (see Table 1). 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 1: 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=6,047 insertions)	1.7 (95% CI: 0.8-3.1; 5,927 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=41,910 insertions)

The risk of perforations may be increased in women with fixed retroverted uterus.

Re-examination after insertion should follow the guidance given under the heading “Medical Examination” (see Section **Error! Reference source not found.**), which may be adapted as clinically indicated in women with risk factors for perforation.

4.4.8 Ectopic pregnancy

Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry an increased risk of ectopic pregnancy. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain - especially in connection with missed periods or if an amenorrhoeic woman starts bleeding. Women who become pregnant while using Jaydess should be evaluated for ectopic pregnancy. The absolute risk of ectopic pregnancy in Jaydess users is low. However, when a woman becomes pregnant with Jaydess *in situ* the relative likelihood of this pregnancy being ectopic is increased and urgent assessment is required (see Section 4.8). In the event of an unplanned pregnancy, see also Section 4.6.2.

The overall incidence of ectopic pregnancy with Jaydess is approximately 0.11 per 100 women-years. This rate is lower than in women not using any contraception (0.3-0.5 per 100 women years).

4.4.9 Sexually transmitted infections (STIs)

Jaydess does not protect against HIV infection (AIDS) and other STIs. Women should be advised that additional measures, e.g. condoms, are needed to prevent the transmission of STIs.

4.4.10 Lost threads

If the removal threads are not visible at the cervix on follow-up examinations, pregnancy must be excluded. The threads may have been drawn up into the uterus or cervical canal and may reappear during the next menstrual period. If pregnancy has been excluded, the threads may usually be located by gently probing the cervical canal with a suitable, sterile instrument. If they cannot be found, the possibility of expulsion or perforation should be considered. Ultrasound exam may be used to ascertain the position of the system. If ultrasound is not available or is not successful, X-ray may be used to locate Jaydess.

4.4.11 Ovarian cysts/enlarged ovarian follicles

Since the contraceptive effect of Jaydess is mainly due to its local effects within the uterus, there is generally no change in ovulatory function, including regular follicular development, oocyte release and follicular atresia 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 and have been reported as adverse reactions in approximately 13.2% of women using Jaydess including ovarian cyst, haemorrhagic ovarian cyst and ruptured ovarian cyst. 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/therapeutic measures may be appropriate. Rarely, surgical intervention may be required.

4.5 Interaction with other medicines and other form of interaction

4.5.1 Effects of other medicines on Jaydess

Interactions can occur with drugs that induce or inhibit microsomal enzymes, which can result in increased or decreased clearance of sex hormones.

Substances increasing the clearance of levonorgestrel, e.g:

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and products containing St. John's wort.

The influence of these drugs on the contraceptive efficacy of Jaydess is not known, but it is not believed to be of major importance due to the local mechanism of action.

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), e.g:

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

4.5.2 Magnetic resonance imaging (MRI)

Non-clinical testing has demonstrated that women may be scanned after placement of Jaydess ('MR conditional') under the following conditions:

- Static magnetic field of 3-Tesla or less,
- Spatial gradient 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 a non-clinical setting under these conditions, the maximum temperature rise at the site of Jaydess was 1.8°C, produced at a maximum whole body averaged specific absorption rate (SAR) of 2.9W/kg, for 15 minutes of MR scanning at 3T using a transit/receive bosy coil. A small amount of imaging artefact may occur if the area of interest is in the exact same area or relatively close to the position of the Jaydess IUS.

No clinical data are currently available in women using Jaydess undergoing MRI.

4.6 Fertility, pregnancy and lactation

4.6.1 Fertility

The use of an LNG-IUS does not alter the course of future fertility. Upon removal of the LNG-IUS, women return to their normal fertility (see Section 5.1).

4.6.2 Pregnancy

Pregnancy Category B3.

The insertion of Jaydess in pregnant women is contraindicated (see Section 4.3).

Because of the intrauterine administration and the local exposure to levonorgestrel, the possible occurrence of virilising effects in a female fetus should be taken into consideration. Clinical experience of the outcomes of pregnancies under Jaydess treatment is limited due to the high contraceptive efficacy. Women should be informed that, to date, there is no evidence of birth defects caused by LNG-IUS use in cases where pregnancy continues to term with the LNG-IUS in place.

4.6.2.1 Unplanned Pregnancy

If a woman becomes pregnant while using Jaydess, removal of the system is recommended since any intrauterine contraceptive left *in situ* may increase the risk of abortion and pre-term labour. Removal of Jaydess or probing of the uterus may also result in spontaneous abortion. Ectopic pregnancy should be excluded. If the woman wishes to continue the pregnancy and the system cannot be withdrawn, she should be informed about the risks and the possible consequences of premature birth to the infant. The course of such a pregnancy should be closely monitored. The woman should be instructed to report all symptoms that suggest complications of the pregnancy, like cramping abdominal pain with fever.

4.6.3 Lactation

In general, there appears to be no deleterious effect on infant growth or development when using any progestogen-only method after six weeks postpartum. An LNG-IUS does not affect the quantity or quality of breast milk. Small amounts of progestogen (about 0.1 % of the levonorgestrel dose) pass into the breast milk in nursing mothers.

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

4.8.1 Summary of the safety profile

The majority of women experience changes in menstrual bleeding pattern after insertion of Jaydess. Over time, the frequency of amenorrhoea and infrequent bleeding increases, and the frequency of prolonged, irregular, and frequent bleeding decreases. The following bleeding patterns were observed in clinical trials with Jaydess:

- During the first 90 day reference period, less than 1% of women experienced amenorrhea, 8% infrequent bleeding, 31% frequent bleeding, 39% irregular bleeding* and 55% prolonged bleeding*.

- During the second 90 day reference period, 3% of women experienced amenorrhea, 19% infrequent bleeding, 12% frequent bleeding, 25% irregular bleeding* and 14% prolonged bleeding*.
- At the end of year 1, 6% of women experienced amenorrhea, 20% infrequent bleeding, 8% frequent bleeding, 18% irregular bleeding* and 6% prolonged bleeding*.
- At the end of year 3, 12% of women experienced amenorrhea, 22% infrequent bleeding, 4% frequent bleeding, 15% irregular bleeding* and 2% prolonged bleeding*.

*Women with irregular and prolonged bleeding may also be included in one of the other categories (excl. amenorrhoea).

4.8.2 Tabulated list of adverse reactions

The frequencies of treatment-emergent adverse events (adverse reactions) reported with Jaydess are summarised in the table below (see Table 2). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The table below reports treatment-emergent adverse events (adverse reactions) by MedDRA system organ classes (MedDRA SOCs). The frequencies are crude incidences of the events observed in clinical trials for the indication contraception in 1672 women (3820.65 women-years).

Frequencies are defined as:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1,000 to < 1/100)
Rare	(≥ 1/10,000 to < 1/1,000)

Table 2: Treatment-emergent adverse events (adverse reactions) in Phase II and III clinical trials

System Organ Class (MedDRA)	Very Common	Common	Uncommon	Rare
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* Vulvovaginitis	Upper genital tract infection Dysmenorrhea Breast pain/ discomfort Device expulsion (complete and partial) Genital discharge	Uterine perforation**	

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

** This frequency is based on a large, prospective, comparative, non-interventional cohort study with women using another LNG-IUS and copper IUDs which showed that breastfeeding at the time of insertion and insertion up to 36 weeks after giving birth are independent risk factors for perforation (see Section 4.4). In clinical trials with Jaydess that excluded breastfeeding women, the frequency of perforation was "rare".

4.8.3 Description of selected adverse reactions

With the use of LNG-IUS, cases of hypersensitivity including rash, urticaria and angioedema have been reported.

If a woman becomes pregnant while using Jaydess, the relative risk of ectopic pregnancy is increased.

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

The following ADRs have been reported in connection with the insertion or removal procedure of Jaydess: procedural pain, procedural bleeding, and insertion-related vasovagal reaction with dizziness or syncope. The insertion or removal procedure may precipitate a seizure in an epileptic patient.

Cases of sepsis (including group A *Streptococcal* sepsis) have been reported following IUD insertion (see Section 4.4).

4.8.4 Special populations

4.8.4.1 Paediatric population

The safety profile of Jaydess in a study with 304 post-menarcheal adolescents was observed to be consistent with that in the adult population.

4.8.5 Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

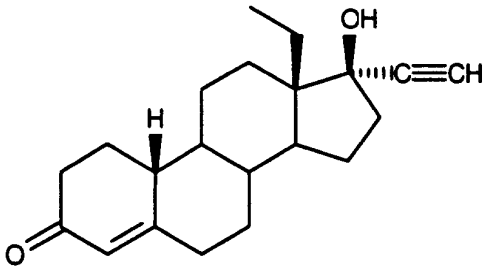
Not applicable for this product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Plastic IUD with progestogen
ATC Code: G02BA03

Levonorgestrel is a white or almost white, odourless or almost odourless, crystalline powder. It is insoluble in water or hexane, slightly soluble in ethanol or acetone, and sparingly soluble in methylene chloride. The chemical name is 13β-ethyl-17β-hydroxy-18, 19-dinor-17α-pregn-4-en-20-yn-3-one. The CAS registry number for levonorgestrel is 797-63-7.



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

Molecular weight: 312.44582 g/mol

Melting Point: 232-239°C

5.1.1 Mechanism of action

Levonorgestrel is a potent progestin of the 19-nortestosterone class which possesses characteristic gestagenic properties such as endometrial transformation (development of a secretory endometrium), antigonadotropic action and antiestrogenic effects. The antiestrogenic activity of levonorgestrel is not the result of direct estrogen antagonism, since levonorgestrel does not bind to the estrogen receptor *in vitro*, but the result of modification of peripheral estrogenic effects. Levonorgestrel does not possess antiandrogenic or glucocorticoid properties, but does have marked partial androgenic activity.

Levonorgestrel is used in gynaecology as the progestogenic component in combined oral contraceptives and for contraception in progestogen-only pills. Levonorgestrel can also be administered into the uterine cavity with an intrauterine delivery system such as Jaydess. This allows a very low daily dosage, as the hormone is released directly into the uterine cavity.

5.1.2 Pharmacodynamic effects

Jaydess has mainly local progestogenic effects in the uterine cavity. The high levonorgestrel concentration in the endometrium down-regulates the endometrial synthesis of estrogen and progesterone receptors. The endometrium becomes relatively insensitive to the circulating estradiol and a strong anti-proliferative effect is seen. Morphological changes of the endometrium and a weak local foreign body reaction 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 fertilisation.

5.1.3 Clinical efficacy and safety

A multicentre, open-label, randomised Phase III study (A52238) was conducted to evaluate the efficacy and safety of two doses of levonorgestrel-releasing IUS in women for long-term reversible contraception. The duration of the study was a maximum of three years for Jaydess with an optional extension phase for the IUS containing the higher dose. A total of 2884 women with an insertion attempt were included in the efficacy and safety assessment of Jaydess and the higher dose LNG IUS (1:1 randomisation).

The contraceptive efficacy of Jaydess has been evaluated in a clinical study with 1432 women aged 18-35 including 38.8% (556) nulliparous women of whom 83.6% (465) were nulligravid using Jaydess. The study evaluated contraceptive efficacy with the following parameters: the number of unintended pregnancies, Pearl Index (PI) and cumulative failure rates, as well as bleeding pattern, pharmacodynamics, pharmacokinetic and safety parameters.

Table 3: PIs by year of treatment for women 18 to 35 years of age, 3-year and Year 1 PIs by subgroup and treatment, unadjusted, study A52238

	No. of women/no. of pregnancies	Relevant exposure time (wy)	Pearl Index (unadj.)	Upper 95% CL
PI by year of treatment and over 3 years, women 18 to 35 years of age[a]				
Year 1 PI	1432 / 5	1217.78	**0.41**	0.96
Year 2 PI	1162 / 3	1015.67	**0.30**	0.86
Year 3 PI	960 / 2	825.17	**0.24**	0.88
3-year PI	1432 / 10	3058.62	**0.33**	0.60

CL = confidence limit, PI = Pearl Index, wy = women years (1 wy = 365 days)
[a] Includes all the women in the study, age range at screening was 18 to 35 years

The one year PI was 0.41 and the PI after 3 years was 0.33 (see Table 3). 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. Because 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 (“perfect use”). The use of Jaydess does not alter the course of the future fertility.
In a Phase II study with 3 different doses of LNG-IUSs including Jaydess (A46796), 25 of 29 women (86.2%) for whom follow up was available wishing to become pregnant conceived within 12 months after removal of the system.

With Jaydess, the alterations in menstrual patterns are a result of the direct action of levonorgestrel on the endometrium and do not reflect the ovarian cycle. There is no clear difference in follicle development, ovulation or estradiol and progesterone production in women with different bleeding patterns. In the process of inhibition of the endometrial proliferation, there can be an initial increase of spotting during the first months of use. Thereafter, the strong suppression of the endometrium results in the reduction of the duration and volume of menstrual bleeding during use of Jaydess. Scanty flow frequently develops into oligomenorrhoea or amenorrhoea. Ovarian function remains normal and estradiol levels are maintained, even when women are amenorrhoeic.

Ovulation was observed in the majority of the subset of women studied (A52238 and A46796). 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.

5.2 Pharmacokinetic properties

Levonorgestrel is released locally into the uterine cavity. Estimated *in vivo* release rates for different points in time are provided in Table 4 below.

Table 4: Estimated *in vivo* release rates for Jaydess

Time	Estimated *in vivo* release rate (µg/24 hrs)
24 days after insertion	14
60 days after insertion	10
1 year after insertion	6
3 years after insertion	5
Average over first year	8
Average over 3 years	6

5.2.1 Absorption

Following insertion, levonorgestrel is released from the IUS into the uterine cavity without delay based on serum concentration measurements. Maximum serum concentrations of levonorgestrel are reached within the first two weeks after insertion of Jaydess. 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. With the use of an levonorgestrel intrauterine delivery system (LNG-IUS), the high local drug exposure in the uterine cavity leads to a strong concentration gradient from the endometrium to the myometrium (gradient endometrium to myometrium >100-fold), and to low concentrations of levonorgestrel in serum (gradient endometrium to serum >1000-fold).

5.2.2 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. Accordingly, the concentration of SHBG in serum affects the free fraction and the total levonorgestrel concentration. Lower SHBG concentrations result in a decrease in the total levonorgestrel concentration in serum and an increase in the proportion of free levonorgestrel. The concentration of SHBG declined by a mean value of approximately 15% during the first month after insertion of Jaydess and remained stable over the 3 year period of use. The mean apparent volume of distribution of levonorgestrel is about 106 L.

Body weight has also been shown to affect systemic levonorgestrel concentration i.e. low body weight increases levonorgestrel concentration.

5.2.3 Biotransformation

Levonorgestrel is extensively metabolised. 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.

5.2.4 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 faeces and urine at an excretion ratio of about 1. The excretion half-life is about 1 day.

5.2.5 Linearity/Non-linearity

The pharmacokinetics of levonorgestrel are dependent on the concentration of SHBG which itself is influenced by estrogens and androgens. A decrease of SHBG concentration leads to a decrease of total levonorgestrel concentration in serum indicating non-linear pharmacokinetics of levonorgestrel with regard to time. Based on the mainly local action of Jaydess, no impact on the efficacy of Jaydess is expected.

5.2.6 Special populations

5.2.6.1 Paediatric population

In a one-year phase III study in post-menarcheal female adolescents (mean age 16.2, range 12 to 18 years) using Jaydess, the pharmacokinetic analysis of 283 adolescents showed estimated levonorgestrel serum concentrations slightly higher (approximately 10%) in adolescents compared to adults. This correlates to the generally lower body weight in adolescents. The

ranges estimated for adolescents lie, however, completely within the ranges estimated for adults, showing high similarity.

No differences in the pharmacokinetics of adolescents and adults are expected with Jaydess.

5.2.6.2 Ethnic differences

A three-year phase III study in the Asian-Pacific region (93 % Asian women, 7 % other ethnicities) using Jaydess has been performed. A comparison of pharmacokinetic characteristics of levonorgestrel of the Asian population in this study with that of the Caucasian population from another phase III study showed no clinically relevant difference in systemic exposure and other pharmacokinetic parameters. In addition, the daily release rate of the LNG-IUS was the same in both populations.

No pharmacokinetic differences in women of different ethnicities are expected with Jaydess.

5.3 Preclinical safety data

5.3.1 Carcinogenicity

No studies on the carcinogenic potential of Jaydess have been performed.

A long-term study with orally administered levonorgestrel in dogs showed an increased incidence of mammary tumours, although a similar effect was not apparent in studies in mice, rats or monkeys. The occurrence of these mammary tumours in dogs may be due in part to a hormonal feedback mechanism. The clinical relevance of these findings is uncertain.

It should be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumours.

5.3.2 Genotoxicity

The genotoxic potential of levonorgestrel has not been fully investigated, although limited data available to date suggest that it does not appear to be genotoxic. Saline, water, ethanol and/or DMSO extracts of the silver ring, elastomer, polyethylene or drug-elastomer components of Jaydess were without mutagenic activity in bacteria. Further assays for genotoxicity (*e.g.*, mouse lymphoma assay, *in vivo* micronucleus test) conducted with extracts of the device materials, were also negative.

5.3.3 Toxicity to reproduction and development

When levonorgestrel-impregnated silastic devices were introduced into the uteri of pregnant rabbits, the incidence of late fetal resorption was increased when compared to sham-operated controls. There were no other effects on the fetuses that could be attributed specifically to the device or to levonorgestrel.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dimethylsiloxane/methylvinylsiloxane cross linked elastomer, colloidal anhydrous silica, polyethylene, barium sulfate, iron oxide black CI77499 and silver.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Not applicable.

6.5 Nature and contents of container

Each pack contains one intrauterine system. Jaydess is packaged in a thermoformed blister package with a peelable lid.

6.6 Special precautions for disposal and other handling

A discarded or removed IUS should be treated as medicinal waste, since it may contain hormone remnants.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.6.1 Instructions for use/handling

Jaydess is supplied in a sterile pack which should not be opened until required for insertion. The exposed product should be handled using aseptic techniques. If the seal of the sterile package is broken, or appears compromised, the product should not be used.

Jaydess is for single use only. Do not re-sterilise. Do not insert after the expiry month and year shown on the label.

Special instructions for insertion are in the package.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Bayer New Zealand Limited

3 Argus Place, Hillcrest

North Shore AUCKLAND 0627

Free phone: 0800 233 988

9. DATE OF FIRST APPROVAL

10 July 2014

10. DATE OF REVISION OF THE TEXT

12 February 2018

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Summary table of changes

Section changed	Summary of new information
All sections	Data Sheet reformatted
3	Additional information regarding the description of Jaydess
4.2	Addition of information regarding paediatric population
4.2	Additional information for women who desire continued contraception, following removal of Mirena
4.4	Additional information from the five year follow-up period for the study regarding perforation
4.5	Addition of interactions with other medicines that can increase the clearance of levonorgestrel, HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, and strong and moderate CYP3A4 inhibitors
4.8	Correction of bleeding pattern data
4.8	Addition of information regarding irregular bleeding
4.8	Update frequency of “uterine perforation” from clinical studies
5.2	Addition of first year and average of first year release rate
5.2	Revised pharmacokinetic information
5.2	Additional pharmacokinetic information regarding paediatric population and ethnic differences
4.8.3	Removal of the word “another” in the statement “With the use of another LNG-IUS, cases of hypersensitivity including rash, urticaria and angioedema have been reported.”