**Mirena 52mg Intrauterine Delivery System** (Levonorgestrel). See full Summary of Product Characteristics (SmPC) before prescribing. **Presentation**: The levonorgestrel intrauterine delivery system (IUD) consists of a white or almost white drug core (52mg Levonorgestrel) covered with an opaque membrane, which is mounted on the vertical stem of a T-body. The T-frame of Mirena contains barium sulphate, which makes it visible in X-ray examination. **Indication**: Contraception, idiopathic menorrhagia, protection from endometrial hyperplasia during oestrogen replacement therapy.
**Dosage and administration**: Insertion into the uterine cavity using aseptic technique by practitioner with experience in Mirena insertion and/or sufficient training. Effective for six years in the indication contraception and five years in the indication idiopathic menorrhagia and protection from endometrial hyperplasia during oestrogen replacement therapy. In women on hormone replacement therapy (HRT), Mirena can be used with oral/transdermal oestrogen preparations without progestogens. Follow full instructions for insertion/removal/replacement, particularly with regard to timing and positioning. Exclude pregnancy, sexually transmitted diseases and endometrial pathology. Treat genital infections. Investigate bleeding irregularities. Re-examine 4 to 12 weeks after insertion and at least once a year. Remove after 6 years in the indication contraception and after 5 years in the indication idiopathic menorrhagia and protection from endometrial hyperplasia during oestrogen replacement therapy. Mid-cycle removal involves a risk of pregnancy unless a new system is inserted immediately. Insertion and removal may be associated with pain, bleeding or a vasovagal reaction. Seizure may be precipitated in an epileptic patient. After removal the device should be checked to be intact. Elderly patients: Mirena has not been studied in women over the age of 65 years. Paediatric population: Safety and efficacy have not been studied in women aged below 18. There is no relevant indication for the use of Mirena before menarche. Hepatic impairment: Mirena is contraindicated in women with acute liver disease or liver tumor. Renal Impairment: Mirena has not been studied in women with renal impairment. **Contraindications**: Known or suspected pregnancy, progestogen-dependent tumours (e.g. breast cancer), current or recurrent pelvic inflammatory disease (PID), cervicitis, lower genital tract infection, postpartum endometritis, infected abortion during the past three months, conditions associated with increased susceptibility to infections, cervical dysplasia, uterine or cervical malignancy, undiagnosed abnormal uterine bleeding, congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity, acute liver disease or liver tumour, hypersensitivity to levonorgestrel or to any of the excipients. **Warnings and Precautions**: Use of Mirena in conjunction with an oestrogen for HRT. If used in conjunction with HRT, the safety information of the oestrogen applies in addition. Use with caution after specialist consultation, consider removal of the system 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 ischemia; exceptionally severe headache; jaundice; marked increase in blood pressure; severe arterial disease such as stroke or myocardial infarction; acute venous thromboembolism. Mirena may be used with caution in women who have congenital heart disease or valvular heart disease at risk of infective endocarditis. The need for antibiotic prophylaxis during insertion and removal of Mirena should be considered in patients with congenital or valvular heart disease. It is recommended that physicians consult local guidelines. Use with caution in postmenopausal women with advanced uterine atrophy. May affect glucose tolerance, monitor blood glucose concentration in diabetic users. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or UV radiation whilst using Mirena. Irregular bleedings may mask some symptoms and signs of endometrial polyps or cancer; consider diagnostic measures. Mirena does not protect against HIV infection (AIDS) and other sexually transmitted diseases. Appropriate diagnostic/therapeutic measures and individual benefit-risk assessment should be undertaken in women with liver cancer. A biological effect on the risk of liver cancer cannot be excluded. Medical examination/consultation: Before insertion, the woman must be informed of the efficacy, risks including signs and symptoms of these risks as described in the Package Booklet and side effects of Mirena. A physical examination including pelvis and breasts should be conducted. Cervical smear should be performed as needed, according to Healthcare Professional's evaluation. Pregnancy and sexually transmitted diseases should be excluded, and genital infections have to be treated. The position of the uterus and the size of the uterine cavity should be determined. Fundal positioning of Mirena is particularly important in order to ensure uniform exposure of the endometrium to the progestogen, prevent expulsion and maximize efficacy. Follow instructions for insertion carefully. Mirena is not suitable for post-coital contraception. Oligo/amenorrhoea: In women of fertile age, oligomenorrhoea and/or amenorrhoea develops gradually in 57% and 16% of women during the first year of use, respectively. By the end of Year 6 of Mirena use, oligomenorrhea and amenorrhea are experienced by 31% and 24% of Mirena users, respectively. The possibility of 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 amenorrhoeic subjects unless indicated by other signs of pregnancy. When Mirena is used in combination with continuous oestrogen replacement therapy, a non-bleeding pattern gradually develops in most women during the first year. If the woman continues the use of Mirena inserted earlier for contraception, endometrial pathology has to be excluded in case bleeding disturbances appear after commencing oestrogen replacement therapy. If bleeding irregularities develop during prolonged treatment, appropriate diagnostic measures should also be taken. Pelvic infection: A decision to use Mirena must include consideration of the risks of PID. In users of copper IUD, the highest rate of pelvic infections occurs during the first month after insertion and decreases later. Known risk factors for PID are multiple sexual partners. PID may have serious consequences and it may impair fertility and increase the risk of ectopic pregnancy. As with other gynae or surgical procedures, sepsis (including with group A streptococcus) can occur rarely following IUD insertion. If the woman experiences recurrent endometritis or pelvic infections or if an acute infection is severe or does not respond to treatment within a few days, Mirena must be removed. Bacteriological examinations are indicated and monitoring is recommended, even with discrete symptoms indicative of infections. Signs and symptoms of PID should be investigated appropriately and treated promptly. Expulsion: Symptoms of the partial or complete expulsion of any IUD may include bleeding or pain; the system can be expelled from the uterine cavity without the woman noticing it leading to loss of contraceptive protection. Partial expulsion may decrease the effectiveness of Mirena. As Mirena decreases menstrual flow, increase of menstrual flow may indicate an expulsion. After expulsion, Mirena may be replaced within 7 days from the onset of the next menstruation. A displaced Mirena should be removed. A new system can be inserted at that time. The woman should be advised how to check the threads of Mirena. 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 Mirena. Such a system must be removed; 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 Mirena cohort and 1.1 (95% CI: 0.7 – 1.6) per 1000 insertions in the copper IUD cohort. 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. Both risk factors were independent of the type of IUD inserted. Extending the observational period to 5 years in a subgroup of this study (N = 39,009 women using Mirena 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. Breastfeeding at the time of insertion and insertion up to 36 weeks were confirmed as risk factors also in this subgroup. The risk of perforation may be increased in women with fixed retroverted uterus. Re-examination after insertion should follow the guidance given under the heading "Medical examination/consultation" which may be adapted as clinically indicated in women with risk factors for perforation. Lost threads: If threads are not visible, exclude pregnancy. If they cannot be found, the possibility of expulsion or perforation should be considered. Ultrasound or, if appropriate, x-ray may be used to ascertain the correct position of Mirena. Breast Cancer: Oral contraceptives, including progestogen-only preparations, are associated with a slightly increased risk of breast cancer. The risk of breast cancer is increased in post-menopausal women using systemic HRT. The risk is higher with combined oestrogen-progestogen HRT than oestrogen-only HRT. Ectopic pregnancy: Women with a previous history of ectopic pregnancy/ tubal surgery / pelvic infection carry a higher risk. 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. In a large prospective comparative non-interventional cohort study with an observation period of 1 year, the ectopic pregnancy rate with Mirena was 0.02%. In clinical trials, the absolute rate of ectopic pregnancies with Mirena was approximately 0.1% per year, compared to 0.3-0.5% per year in women not using any contraception. The relative likelihood of ectopic pregnancy is increased if pregnancy occurs with Mirena in situ. Ovarian Cysts: Delayed follicular atresia may occur and folliculogenesis may continue. Ovarian cysts may be accompanied by pelvic pain/dyspareunia. Should they not disappear spontaneously, continue ultrasound monitoring and other diagnostic/therapeutic measures. Rarely, surgical intervention may be required. Psychiatric Disorders: Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use. Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment. **Interactions:** The prescribing information of concomitant medications should be consulted to identify potential interactions. 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 efficacy of Mirena 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. **Fertility, pregnancy and lactation:** Pregnancy**:** If pregnancy occurs, removal of the system is recommended. IUS left in situ, removal of Mirena or probing of the uterus may increase the risk of spontaneous abortion or preterm labour. Exclude ectopic pregnancy. If Mirena cannot be gently removed, inform the woman about the risks and possible consequences and monitor pregnancy closely. Teratogenicity cannot be completely excluded. Clinical experience of pregnancy under Mirena is limited. Lactation: Levonorgestrel blood concentrations are lower with Mirena than any other hormonal contraceptive. Levonorgestrel has been identified in breast milk (about 0.1%) but it is not likely that there will be a risk for the child with the dose released from Mirena. Uterine bleeding is rarely reported during use in lactation. Fertility: Upon removal of Mirena, women return to their normal fertility. **Effects on ability to drive and use machines**: No studies on the ability to drive and use machines have been performed. **Undesirable Effects:** Very common: headache, abdominal/pelvic pain, bleeding changes including increased and decreased menstrual bleeding, spotting, oligomenorrhoea and amenorrhoea, vulvovaginitis, genital discharge. Common: depressed mood/depression, libido decreased, migraine, dizziness, nausea, acne, hirsutism, back pain, upper genital tract infection, ovarian cyst, dysmenorrhoea, breast pain, intra-uterine contraceptive device expelled (complete and partial), weight increase. Uncommon: alopecia, chloasma/skin hyperpigmentation, uterine perforation. Unknown frequency: hypersensitivity including rash, urticaria and angioedema, blood pressure increased. **Marketing Authorisation Number: PA 1410/008/001**. **Marketing Authorisation Holder/ Further information available from**: Bayer Limited, The Atrium, Blackthorn Road, Dublin 18, Ireland. Tel.: (01) 2163300. **Classification for sale or supply**: prescription only. **Date of preparation:** February 2021.