# Application for inclusion of Implantable contraceptives in the WHO List of Essential Medicines

## 1. Summary statement of the proposal for inclusion, change or deletion

Etonogestrel releasing implant (Implanon®) and levonorgestrel releasing implant (Jadelle®) are two low-dose progestogen-only implants. These are small 2-3cm rods, inserted sub-cutaneously in the upper arm. In addition to being highly effective, they are also cost-effective, have a long life-span, a minimal need for medical follow-up, offer low and stable hormone levels and therefore minimize metabolic effects and provide a rapid return to fertility once discontinued. Failure rates for implants are equivalent to those of sterilization \(^1\). Acceptability is comparable to other contraceptives; the most common reason for discontinuation is menstrual disturbance. Complications are rare and most common side effects are: changes in bleeding pattern, headache, weight gain, acne, lower abdominal pain and dizziness. Implantable contraceptives are registered in over 60 countries worldwide.

## 2. Name of the focal point in WHO submitting application


## 3. Name of the organization consulted and supporting the application

The Geneva Foundation for Medical Education and Research (GFMER; http://www.gfmer.ch/) is submitting the application. GFMER is a WHO Collaborating Centre in Education and Research in Human Reproduction. Staff at GFMER has extensive experience in conducting systematic reviews, critically appraising the literature and developing recommendations.

## 4. International Nonproprietary Name (INN, generic name) of the medicine

- Levonorgestrel releasing implant (Jadelle®)
- Etonogestrel releasing implant (Implanon®)
5. Whether listing is requested as an individual medicine or as an example of a therapeutic group
Listing as two individual medicines

6. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Implantable contraceptives increase the choice for contraceptive methods by providing effective, reversible long-term protection. Implantable contraceptives are registered in over 60 countries and have been used by some 11 million women for about 30 years \(^{(2)}\). Jadelle® is registered in the USA and in some European Union (EU) countries. Implanon® is registered in several countries worldwide (EU, Australia, Canada, Indonesia and Switzerland).

7. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

- **Dosage regimen:**
  1. JADELLE® consists of two implantable rods, each containing 75 mg of Levonorgestrel, a second generation progestogen. The release rate of Levonorgestrel is about 100 µg/day during the first month, 40 µg/day after one year and stabilizes at 30 µg/day after two years \(^{(3)}\).
  2. IMPLANON® consists of a single rod containing 68 mg of etonogestrel (a metabolite of desogestrel-a third generation progestogen). The release rate of etonogestrel is 60 µg/day in the beginning and 30 µg/day after two years \(^{(4)}\).

- **Duration:** 5 years for Jadelle® and 3 for Implanon®
- **Diagnostic:** for reversible contraceptive use
- **Treatment facilities:** The implant should be inserted during the first 7 days (for Jadelle®) and first 5 days (for Implanon®) of the cycle by a health-care professional trained in the insertion technique. Implants are usually inserted subdermally in the non dominant arm approximately 6-8 cm above the elbow \(^{(5)}\).
8. Summary of comparative effectiveness in a variety of clinical settings:

- Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

The Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, Popline and Lilacs were systematically searched; specialists in the field were contacted to identify any ongoing or unpublished data. Most of the data on the effectiveness of Jadelle® and Implanon® are from large cohort rather than from randomized controlled trials.

Contraceptive effectiveness
Levonorgestrel-containing implants, such as Jadelle®, prevent normal sperm transport, impair the normal endometrial development and inhibit ovulation to some degree; Implanon® mainly suppresses ovulation. A multicentric study undertaken in different countries reported no pregnancies with Jadelle® during the first four years and a 1% pregnancy rate (6 women) during the fifth year of use among 600 women selected for the study. Jadelle® has been found to be as effective in preventing pregnancy as the LNG-releasing IUD. The rate of ectopic pregnancies during Jadelle® use has been reported at 0.4%, which gives an 80%-90% reduction in the risk of ectopic pregnancy compared to the risk among women using no contraceptive method.

Data from 13 studies showed no pregnancies with Implanon® during 4103 women-years. However, these studies excluded obese women. Similar results regarding effectiveness were reported from studies conducted in South America, Indonesia and China.

Continuation rate and reason for discontinuation
Bleeding irregularities are common in progestogen-containing implant users and although they are not hazardous for a woman’s health, they can influence the continuation rate. A 5-year randomized controlled trial conducted in the USA, Chile, Thailand, Finland, Singapore and Egypt including 600 women, reported continuation rates of 71% after 3 years, 63% after 4 years and 55% after 5 years for Jadelle®. The main reason for discontinuation was menstrual disturbances (including...
amenorrhea). The cumulative 5-year discontinuation rates for menstrual disturbances were 16.4% and 15% for other medical reasons (headaches, weight gain and acne). A study comparing Jadelle® with the LNG-releasing IUD showed no difference in discontinuation rates between the two methods\(^{(12)}\).

Differences in continuation rates according to countries have been reported, reflecting the difference of method-acceptability in various cultural settings\(^{(6)}\). In a review of bleeding patterns among implant users, great variations in continuation rates of Implanon® were reported: among 1716 Implanon® users, 30.2% of women in Europe and Canada had discontinued after 3 years compared to 0.9% in South Asia\(^{(13)}\). Bleeding irregularities were the most common reasons for discontinuation. Amenorrhea was found in 30-40% of Implanon® users after the first 3 months with about 50% experienced infrequent bleeding, a proportion which decreased to 30% after 6 months\(^{(28)}\). Discontinuations have been found to occur more frequently during the first year of Implant use\(^{(14)}\).

Return to fertility
Both implants release low doses of progestogen that clear rapidly once the implant is removed allowing a fast return to normal cycles. Ovulation and fertility are reported to return approximately after 3 months following implant removal\(^{(15,16)}\). A study comparing Jadelle®, a levonorgestrel (LNG) -releasing IUD and a copper IUD (TCu380 Ag) reported a pregnancy rate at 2 years of 92% for Jadelle® and 88% for both other methods\(^{(17)}\). A pilot study on Implanon® conducted in Thailand showed that 6 women out of 29 became pregnant in the three months following Implanon® removal\(^{(16)}\).

- **Summary of available estimates of comparative effectiveness**
Jadelle® and Implanon® seem to be equally effective and comparable to other commonly used long-term hormonal contraceptives and female sterilization.
9. Summary of comparative evidence on safety:

- **Estimate of total patient exposure to date to implant contraceptives**
  Implants have been used by about 11 million women over the last 3 decades \(^{(2)}\). In Indonesia, 3 million women use an implant, which represents 11% of all women using contraception \(^{(19)}\).

- **Description of adverse effects/reactions**
  The most common side effects of implantable contraceptives are menstrual disturbances reported as the first reason for discontinuation (up to 45% of all reasons reported) \(^{(1)}\). These are more common in the first months and tend to diminish over time. Other side effects are: headache (21-23%), weight gain (7-12%), acne (6-19%), lower abdominal pain (11-17%) and dizziness (8-11%). Other complaints reported by a small proportion of women are: mood changes, nausea, breast tenderness, pelvic pain and loss of libido \(^{(18,19)}\).

  An overview of observational studies on the safety of implants found no higher risk of adverse events in implant users compared to non-users \(^{(25)}\). Specifically, no increased risk for pelvic inflammatory disease, decreased bone mineral density, anemia, thrombocytopenia, or death was found in implant users. The data in this review did not allow to draw conclusions for neoplastic disease, cardiovascular events and impact on HIV/AIDS \(^{(25)}\). Studies on metabolic effects of implantable contraceptives conducted in healthy women showed minimal changes within the normal limits for metabolic parameters \(^{(26)}\).

- **Identification of variation in safety due to health systems and patient factors**
  For a safe use of implant contraceptives, technical quality of care has to be provided. It includes trained personnel to check the women’s health and insert the implant, asepsis maintenance and sufficient supplies of insertion trochars. Studies on implants seem to prove their safety, but available data are not sufficient to allow full safety assessment as there is a lack of data on women with certain medical conditions \(^{(20)}\). Furthermore, efficacy studies of Implanon® among women weighing over 80 kg are lacking. For Implanon®, some questions, such as the window in the
cycle during which implant use can safely begin, the delay after insertion until a reliable protection against pregnancy is obtained and the time to return to fertility after removal still need to be addressed (21). The incidence of infection or expulsion following implant insertion is very rare (0-0.5%) (20).

Similar to other progestogen-containing contraceptives, progestogen-containing implants should not be used in the following situations: pregnancy; breastfeeding <6 weeks postpartum; current deep venous thrombosis or pulmonary embolism; unexplained vaginal bleeding; current and past breast cancer; active viral hepatitis; severe cirrhosis; benign and malignant liver tumors; use of drugs affecting liver enzymes (Rifampicin and certain anticonvulsants) (22).

Contraceptive implants should be removed in case of current and history of ischemic heart disease or stroke; migraine with aura at any age; acute or chronic hepatic dysfunction (22). Women with cervical, endometrial and ovarian cancer, while awaiting treatment, may use progestogen implants (22). Some progestogen-only contraceptives can increase the risk of contracting thrombosis; nevertheless the risk is much lower than with combined oral contraceptives (22).

- **Summary of comparative safety against comparators**
  Progestogen-containing implants provide a safe and reliable method of contraception. Serious adverse effects are rare.

10. **Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group**

- **Range of costs of the proposed medicine**
  Implanon® costs approximately 180 USD for three years in France and 260 USD in Switzerland. The public sector costs for Implanon® are 37 USD and for Jadelle® 27 USD plus 8 USD for the trochar.

- **Comparative cost-effectiveness presented as range of cost per routine outcome**
  The public sector cost for Progestin-only injections are 3.5 USD per year.
LNG-releasing IUD cost 40 USD in the public sector for 5 years and varies from 160 to 270 USD in the private sector.

11. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Jadelle® is approved for five years of use in a number of countries, including several European countries and the USA (23). Implanon® is approved for three years of use in EU, Australia, Canada, Indonesia and Switzerland (23).


British Pharmacopoeia: requested
International Pharmacopoeia: requested
United States Pharmacopoeia: requested

13. Proposed (new/updated) text for the WHO Model Formulary

• JADELLE® Levonorgestrel-releasing implant
• IMPLANON® Etonogestrel-releasing implant

Use: hormonal contraception
Contraindications (22): pregnancy; breastfeeding <6 weeks postpartum; current deep venous thrombosis or pulmonary embolism; unexplained vaginal bleeding; current and past breast cancer; active viral hepatitis; severe cirrhosis; benign and malignant liver tumors; use of drugs affecting liver enzymes (Rifampicin and certain anticonvulsants). Stop using contraceptive implant in case of current and history of ischemic heart disease or stroke; migraine with aura at any age.

Precautions: diabetes; breast nodules, or an abnormal breast x-ray or mammogram; diabetes; elevated cholesterol or triglycerides; high blood pressure; migraine or other headaches; epilepsy; mental depression; gallbladder, heart, or kidney disease; or a history of blood clots, heart attack, or stroke (24).

Administration: Insertion of the implant should be performed during the first 7 days (Jadelle®) and 5 days (Implanon®) after the onset of menses by a health-care professional expert in the insertion technique. Implants can be inserted sub-dermally in the non dominant arm approximately 6-8 cm above the elbow.
**Side effects**: The most common side effects of implantable contraceptives are menstrual disturbances. Less common side effects are: headache, weight gain, acne, lower abdominal pain and dizziness. Very rare side effects are: mood changes, nausea, breast tenderness, pelvic pain and loss of libido\(^{(19)}\).

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**References**


5. Implanon. Information médicale du Compendium suisse des médicaments. 2004


17 Sivin I, Stern J, Diaz S et al. (1992) Rates and outcomes of planned pregnancy after use of Norplant capsules, Norplant II rods, or levonorgestrel-releasing or copper TCu 380 Ag intrauterine contraceptive devices. American Journal of Obstetrics and Gynecology 166:1208-13
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