

**Application for inclusion of  
Levonorgestrel - releasing implantable contraceptives  
in the WHO List of Essential Medicines**

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

Levonorgestrel-releasing implants consist of small 2-3cm rods which are inserted subcutaneously 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.

The previously marketed six-rod containing implant (Norplant®) has been tested in many studies but failed to gain popularity because of its relatively high cost and difficulties during removal (2). The two-rod containing subdermal implant has been shown to be as effective as the six-rod one but is easier to insert and to remove (3).

Implantable contraceptives are widely used and are currently registered in over 60 countries. An earlier application for inclusion of low-dose progestogen-releasing implants into the WHO Essential Medicines list was rejected by the WHO Expert Committee after consideration of the balance of benefits, harms and the need for additional contraceptive choice and the relatively high cost and training needed to insert and remove the device. The current application is based on the fact that new information to address the issues raised on cost and training has become available.

Data now show that implants are highly cost-effective and the initial higher costs should not be a barrier for use (4).

There is a need for training when placing contraceptive devices in general. However, the procedure for implants can be easily adopted by health care professionals and may require less training than for placement of other devices (i.e. intra-uterine devices), which is reflected in the low complication rates for inserting and removing implants (2,5). Implants provide a reliable, reversible long-acting contraceptive alternative to IUDs.

Implantable contraceptives provide an effective and safe family planning method and increase the available options of contraceptives offered to women worldwide.

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

Dr. Catherine d’Arcangues, Coordinator, UNDP/UNFPA/WHO/ WHO Special Programme of Research, Development and Research Training in Human Reproduction, Department of Reproductive Health and Research, Family and Community Health Cluster (WHO/RHR).

**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 along with Family Health International (FHI; <http://www.fhi.org>). 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. FHI has worked for more than 30 years to improve the availability, safety, acceptance, and use of modern contraceptive methods. FHI has extensive experience with the regulatory approval of new contraceptive methods as well as conducting clinical and behavioral research of existing methods, including contraceptive implants.

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

Two-rod levonorgestrel-releasing implant

**5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)**

Two-rod levonorgestrel-releasing implant; each rod containing 75 mg of levonorgestrel (150 mg total)

**6. International availability - sources, if possible manufacturers**

Jadelle® (manufactured by Schering Oy) is registered in the USA and in some European Union (EU) countries. Sino-implant No. 2 is manufactured by Shanghai Dahua Pharmaceutical in China and is registered in China and Indonesia.

**7. Whether listing is requested as an individual medicine or as an example of a therapeutic group**

Listing as an individual medicine

## 8. 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 (6).

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

- **Dosage regimen:**
- The implant consists of two implantable Silastic rods, each containing 75mg 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 (7).
- **Duration:** 5 years for Jadelle; 4 years for Sino implant No. 2 (with possible extension to 5 years based on comparative clinical data)(8)
- The conditions under which implantable contraceptives are appropriate are outlined in the WHO *Medical eligibility criteria for contraceptive use*, which form part of a series of evidence-based documents for family planning produced by WHO/RHR together with an international working group and provides recommendations for use of contraceptive methods for different conditions (9). The second cornerstone of this series, the *Selected practice recommendations for contraceptive use*, refers to the practical use of family planning methods. In its latest edition it addresses 33 questions, 3 of them are related to the use of implantable contraceptives (10). These provide answers to questions such as ‘*when can a woman start using an implant*’ and ‘*what can be done if a woman experiences menstrual abnormalities when using an implant*’.

The third and fourth cornerstones, a decision-making tool for family planning clients and providers and a handbook for family planning providers (11), are practical tools for service providers.

- **Diagnostic:** for reversible contraceptive use.  
Pregnancy should be excluded before starting any contraceptive method. A checklist for providers is included in the *Selected practice recommendations for contraceptive use* (10). This checklist enables providers to be ‘*reasonably sure*’ that pregnancy is excluded. In addition,

services providing family planning should aim to provide adequate information for clients and training of providers (9).

- **Treatment facilities:** The implant should be inserted during the first 7 days of the cycle by a health-care professional trained in the insertion technique (9). Implants are usually inserted sub-dermally in the non-dominant arm approximately 6-8 cm above the elbow (7). The insertion and removal procedure is generally easily adopted by health care professionals, which is reflected in the low complication rates reported (12,5)

Follow-up: No routine follow-up is required; advice should be given when to return for removal of the implant (10).

## 10. 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.

### Contraceptive effectiveness

Levonorgestrel-containing implants create changes in cervical mucus that make it hostile to sperm and prevent normal sperm transport, impair the normal endometrial development and inhibit ovulation to some degree (13). In 1990, the 6-rod levonorgestrel-releasing implant (Norplant®) was approved by FDA for contraceptive use. Norplant® has been shown to be highly effective and safe (14). In order to reduce the number of rods and allow for easier insertion and removal, a two-rod implant was designed. In a study comparing Norplant® with the two-rod implant in 1200 women over a 5-year follow-up period, the cumulative pregnancy rate after 5 years was 1 per 100 users for the two-rod implant and 0.7 per 100 users for Norplant®(12). This failure rate of  $\leq 1$  is comparable to that for female sterilization (1).

Compared to other long-acting reversible contraceptives, Jadelle® has been found to be as effective in preventing pregnancy as the LNG-releasing IUD (15).

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 (12).

A multicenter comparative clinical study comparing Norplant® with Sino-implant No. 2 in 1998 women reported a cumulative five-year pregnancy rate of 0.7 per 100 women in the two-rod implant group compared with 0 pregnancies per 100 women in the Norplant® group (8).

#### Continuation rate and reason for discontinuation

Bleeding irregularities are common in progestogen-only-contraceptive users and although they are not hazardous for a woman's health, they can influence the continuation rate. After sterilization, implantable contraceptives showed the highest continuation rate among couples attempting to avoid pregnancy during 1 year (16). 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® which is comparable to other long-term reversible contraceptives (12). 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 (17).

Differences in continuation rates according to countries have been reported, reflecting the difference of method-acceptability in various cultural settings (12).

#### Return to fertility

Jadelle® releases low doses of progestogen that clear rapidly once the implant is removed allowing a fast return to normal cycles.

A study comparing Jadelle®, a levonorgestrel (LNG) -releasing IUD and a copper IUD (TCu380 Ag) reported a pregnancy rate at 2 years after discontinuation of 92% for Jadelle® and 88% for both other methods (18).

- **Summary of available estimates of comparative effectiveness**

Levonorgestrel releasing implants are equally or more effective and comparable for their discontinuation rates to other long-term hormonal contraceptives, intrauterine devices, and vasectomy and female sterilization (16). They allow for long-term contraceptive protection and low dose-steroid exposure.

## 11. 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 (6). In Indonesia, 3 million women use an implant, which represents 11% of all women using contraception (19).

- **Description of adverse effects/reactions**

**Side effects:** As for any progestogen-only contraceptive method, changes in bleeding pattern are common mainly during the first months of use. 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%). A small proportion of women reported mood changes, nausea, breast tenderness, pelvic pain and loss of libido (19, 20).

**Safety:** Several studies and overviews of studies conducted by WHO and its partners confirmed the safety of levonorgestrel-releasing implants (14, 21, 22, 23, 24, 25). One overview of observational studies found no higher risk of adverse events in implant users compared to non-users (21). Specifically, no increased risk for pelvic inflammatory disease, decreased bone mineral density, anemia, thrombocytopenia, or death was found in implant users. There is limited evidence to allow any meaningful conclusions regarding neoplastic disease (14, 21) and impact on HIV/AIDS (21).

### Metabolic effects and non-reproductive health events

Norplant® has been studied extensively for its impact on metabolic changes (14, 22). Two-rod levonorgestrel releasing implant has been shown to be equivalent to Norplant® (26) therefore making metabolic data on Norplant® relevant for this application.

The UNDP/UNFPA WHO Special Programme of Research, Development and Research Training in Reproductive Health, conducted a study in 177 Norplant users compared to 174 copper-IUD users and found that the effect of Norplant on the lipid metabolism is limited and does therefore not increase the risk for cardiovascular disease (27). In a post marketing surveillance study conducted by WHO, including almost 8000 women followed for up to 5 years, no significant excess risk for stroke, myocardial infarction, or venous thrombo-embolism was observed in Norplant® users compared to non-hormonal contraceptive users (14). There was a slight increase in gallbladder disease in women using Norplant® (rate ratio 1.52) – this weak association has also been reported with the use of combined oral contraceptives previously (14).

An increase in borderline hypertension in the Norplant® group may have been partially due to reporting bias in this group, as blood pressure measurements were more frequently in this group (14). Two reviews of metabolic studies did not find a significant excess risk of diabetes in women using Norplant® compared to non-hormonal contraception users (14, 28).

An overview of studies on metabolic effects of implantable steroid contraceptives reported minimal changes within the normal limits for metabolic parameters in healthy women (22).

**Safety related to insertion and removal:** Insertion and removal can cause discomfort, but technical problems occur in < 1/100 procedures (29). Among 600 women, the mean removal time was 4.8 minutes for the two-rod device compared to 9.6 minutes for the 6-rod device (Norplant®). Duration of use was not related to difficulty of removal (12). The incidence of infection or expulsion following implant insertion is very rare (0-0.5%) (23).

- **Identification of variation in safety due to health systems and patient factors**

For 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 devices.

Studies on implants seem to prove their safety and criteria for use in women with certain medical conditions have been outlined in the *WHO Medical Eligibility Criteria* (9).

Similar to other progestogen-containing contraceptives, progestogen-releasing 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) (9).

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 (9).

Women with cervical, endometrial and ovarian cancer, while awaiting treatment, may use progestogen implants (9). Some progestogen-only contraceptives can increase the risk of contracting thrombosis; nevertheless the risk is much lower than with combined oral contraceptives (9).

- **Summary of comparative safety against comparators**

Progestogen-containing implants provide a safe and reliable method of contraception. Serious adverse effects are rare. Overall, the incidence of adverse events among implant users is low and does not differ from rates in non-hormonal controls (14, 21).

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

- **Range of costs of the proposed medicine**

The public sector cost for Jadelle® is 21 USD per set.

The quoted wholesale price for Sino implant No. 2 is 4.50 USD per set.

- **Comparative cost-effectiveness presented as range of cost per routine outcome**

The National Institute for Health and Clinical Excellence (NICE) in its report from 2005 states that among the four long-acting reversible contraceptive methods (LARC) IUD, IUS and implant are the most cost effective ones, and are becoming more cost effective with longer duration of use. This means that the relatively high initiation costs should not be a barrier to their use, as LARC result in greatest cost-savings compared to other reversible methods (4). This report further states that all currently available LARC methods (intrauterine devices [IUDs], the intrauterine system [IUS], injectable contraceptives and implants) are more cost effective than the combined oral contraceptive pill even at 1 year of use.

## **13. 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 (4).

Sino-implant No. 2 is approved for four years of use in China and Indonesia.

## **14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)**

Jadelle®:

British Pharmacopoeia: requested

United States Pharmacopoeia: requested

Sino-implant No. 2:

China Pharmacopoeia, 2000 edition

## **15. Proposed (new/updated) text for the WHO Model Formulary**

- Two-rod -levonorgestrel-releasing implant

**Use:** hormonal contraception

**Contraindications** (9): 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 (30).

**Administration:** Insertion of the implant should be performed during the first 7 days after the onset of menses by a health-care professional trained in the insertion technique. Implants can be inserted sub-dermally in the non dominant arm approximately 6-8 cm above the elbow. The insertion technique requires little training and can be easily adopted by clinical practitioners

**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 (21).

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