National Essential Medicine List Medication Review Process Primary Healthcare
Component: Family Planning

Date of review: 19 April 2013

Medication names: Etonogestrel and levonorgestrel subdermal implants

Indication: Long-acting reversible contraception

Introduction: [1 2 3]
The levonorgestrel implant consists of two rods (approximately 43mm in length and 2.5mm in diameter) each containing 75mg of levonorgestrel and a siloxane copolymer enclosed in thin-walled silicone tubing. Levonorgestrel is released at a rate of about 100mcg/day at one month, 40mcg/day at 12 months, 30mcg/day 24 months with stabilisation thereafter at about 30mcg/day. The levonorgestrel implant is effective for up to 5 years of use. The contraceptive effects include inhibition of ovulation and thickening of the cervical mucus.

The etonogestrel implant consists of a single-rod (40mm in length and 2mm in diameter) containing 68 mg of etonogestrel dispersed in a membrane of ethylene vinyl acetate. Etonogestrel is released at a rate of approximately 60-70mcg/day in week 5-6, decreasing to approximately 35-45mcg/day at the end of the first year, 30-40mcg/day at the end of the second year and 25-30mcg/day at the end of the third year. The etonogestrel implant is effective for up to 3 years of use. The contraceptive effects include inhibition of ovulation, inhibition of endometrial proliferation and thickening of the cervical mucus

The aim of this review is to evaluate the effectiveness and safety of the two-rod levonorgestrel and single-rod etonogestrel subdermal implants for consideration for inclusion on the National Essential Medicines List as additional long-acting reversible contraceptive methods to the copper intrauterine contraceptive device. The primary effectiveness outcome measure is defined as the rate of pregnancy.

At the time of this review, the etonogestrel single-rod subdermal implant was under review for registration in South African by the Medicines Control Council *i.e.* Implanon NXT®.

The review of levonorgestrel subdermal implants will be limited to studies that include the two-rod levonorgestrel-releasing implant recently registered in South Africa by the Medicines Control Council *i.e.* Jadelle®.

The literature review identified studies pertaining to other two-rod implants. The implant of Chinese manufacture, Sino-plant II®, has the same amount of active ingredient as Jadelle® but is effective for up to 4 years of use. Sino-plant II® is however not registered for use in South Africa. Jadelle® replaced Norplant II® and differs to the prototype in terms of the silicone elastomer in the core, total drug load and diameter of each rod.

There is evidence to support the higher effectiveness of intrauterine contraceptive devices (IUCDs) having larger copper surface areas. This review will be limited to comparative studies of copper IUCDs with a surface area $\geq$ 375 mm^2.

Search strategy and selection of studies:
Electronic literature surveys using the following terminology were performed (database: PUBMED):

Levonorgestrel subdermal implant
("levonorgestrel"[MeSH Terms] OR "levonorgestrel"[All Fields]) AND ("contraceptive agents"[MeSH Terms] OR ("contraceptive"[All Fields] AND "agents"[All Fields]) OR "contraceptive agents"[All Fields] OR "contraceptive"[All Fields] OR "contraceptive agents"[Pharmacological Action] OR "contraceptive devices"[MeSH Terms] OR ("contraceptive"[All Fields] AND "devices"[All Fields]) OR "contraceptive devices"[All Fields]) AND implant[All Fields] AND rod[All Fields] NOT ("3-keto-desogestrel"[Supplementary Concept] OR "3-keto-desogestrel"[All Fields] OR "implanon"[All Fields]) AND (Randomized Controlled Trial[ptyp] AND English[lang])

This returned 5 studies; of which 2 studies were randomized and found to be relevant to the aim of the review and fulfilled the requirements for inclusion in the review.

Etonogestrel subdermal implant
("3-keto-desogestrel"[Supplementary Concept] OR "3-keto-desogestrel"[All Fields] OR "etonogestrel"[All Fields]) OR ("3-keto-desogestrel"[Supplementary Concept] OR "3-keto-desogestrel"[All Fields] OR "implanon"[All Fields]) OR ("3-keto-desogestrel"[Supplementary Concept] OR "3-keto-desogestrel"[All Fields] OR "3 keto desogestrel"[All Fields]) AND ("contraceptive agents"[MeSH Terms] OR

("contraceptive"[All Fields] AND "agents"[All Fields]) OR "contraceptive agents"[All Fields] OR "contraceptive"[All Fields] OR "contraceptive agents"[Pharmacological Action] OR "contraceptive devices"[MeSH Terms] OR ("contraceptive"[All Fields] AND "devices"[All Fields]) OR "contraceptive devices"[All Fields]) AND implant[All Fields] AND ((Randomized Controlled Trial[ptyp] OR Multicenter Study[ptyp]) AND English[lang])

This returned 31 studies, of which only 1 study was randomized and found to be relevant to the aim of the review and fulfilled the requirements for inclusion in the review.

Comparing levonorgestrel and etonogestrel subdermal implants

"levonorgestrel"[MeSH Terms] OR "levonorgestrel"[All Fields]) AND (("3-keto-desogestrel"[Supplementary Concept] OR "3-keto-desogestrel"[All Fields] OR "etonogestrel"[All Fields]) OR ("3-keto-desogestrel"[Supplementary Concept] OR "3-keto-desogestrel"[All Fields] OR "implanon"[All Fields]) OR ("3-keto-desogestrel"[Supplementary Concept] OR "3-keto-desogestrel"[All Fields] OR "3 keto desogestrel"[All Fields])) AND ("contraceptive agents"[MeSH Terms] OR ("contraceptive"[All Fields] AND "agents"[All Fields]) OR "contraceptive agents"[All Fields] OR "contraceptive"[All Fields] OR "contraceptive agents"[Pharmacological Action] OR "contraceptive devices"[MeSH Terms] OR ("contraceptive"[All Fields] AND "devices"[All Fields]) OR "contraceptive devices"[All Fields]) AND implants[All Fields] AND rod[All Fields] AND English[lang]

This returned 15 studies identifying only 1 study relevant to the aim of the review. The study was an open, parallel group trial comparing etonorgestrel and the two-rod levonorgestrel implants (randomized) and the copper IUCD with a surface area $\geq$ 375 mm^2 (non-randomized) was identified.

Comparing the levonorgestrel subdermal implant with the copper IUCD and/or levonorgestrel intrauterine system

("levonorgestrel"[MeSH Terms] OR "levonorgestrel"[All Fields]) AND ("contraceptive agents"[MeSH Terms] OR ("contraceptive"[All Fields] AND "agents"[All Fields]) OR "contraceptive agents"[All Fields] OR "contraceptive"[All Fields] OR "contraceptive agents"[Pharmacological Action] OR "contraceptive devices"[MeSH Terms] OR ("contraceptive"[All Fields] AND "devices"[All Fields]) OR "contraceptive devices"[All Fields]) AND implants[All Fields] AND ("intrauterine devices"[MeSH Terms] OR ("intrauterine"[All Fields] AND "devices"[All Fields]) OR "intrauterine devices"[All Fields]

OR ("intrauterine"[All Fields] AND "device"[All Fields]) OR "intrauterine device"[All Fields]) AND (Randomized Controlled Trial[ptyp] AND English[lang])

This returned 8 studies none of which were eligible for inclusion in the review.

A second survey was conducted without the randomized controlled trial filter using the following strategy:

("levonorgestrel"[MeSH Terms] OR "levonorgestrel"[All Fields]) AND implants[All Fields] AND ("intrauterine devices"[MeSH Terms] OR ("intrauterine"[All Fields] AND "devices"[All Fields]) OR "intrauterine devices"[All Fields] OR ("intrauterine"[All Fields] AND "device"[All Fields]) OR "intrauterine device"[All Fields]) AND ("contraceptive agents"[MeSH Terms] OR ("contraceptive"[All Fields] AND "agents"[All Fields]) OR "contraceptive agents"[All Fields] OR "contraceptive"[All Fields] OR "contraceptive agents"[Pharmacological Action] OR "contraceptive devices"[MeSH Terms] OR ("contraceptive"[All Fields] AND "devices"[All Fields]) OR "contraceptive devices"[All Fields]) NOT ("3-keto-desogestrel"[Supplementary Concept] OR "3-keto-desogestrel"[All Fields] OR "implanon"[All Fields]) NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "reviews"[All Fields]) AND English[lang]

This retrieved 87 studies of which 1 study was found to be relevant to the aim of the review. An open, parallel group trial comparing the single-rod etonogestrel and two-rod levonorgestrel subdermal implants (randomized) and the copper IUCD with a surface area $\geq$ 375 mm^2 (non-randomized) was identified.

Comparing the etonogestrel subdermal implant with the copper IUCD and/or levonorgestrel intrauterine system

("3-keto-desogestrel"[Supplementary Concept] OR "3-keto-desogestrel"[All Fields] OR "etonogestrel"[All Fields]) OR ("3-keto-desogestrel"[Supplementary Concept] OR "3-keto-desogestrel"[All Fields] OR "implanon"[All Fields]) OR ("3-keto-desogestrel"[Supplementary Concept] OR "3-keto-desogestrel"[All Fields] OR "3 keto desogestrel"[All Fields]) AND ("contraceptive agents"[MeSH Terms] OR ("contraceptive"[All Fields] AND "agents"[All Fields]) OR "contraceptive agents"[All Fields] OR "contraceptive"[All Fields] OR "contraceptive agents"[Pharmacological Action] OR "contraceptive devices"[MeSH Terms] OR ("contraceptive"[All Fields] AND "devices"[All Fields]) OR "contraceptive devices"[All Fields]) AND implants[All Fields] AND ("intrauterine devices"[MeSH Terms] OR ("intrauterine"[All Fields] AND

"devices"[All Fields]) OR "intrauterine devices"[All Fields] OR ("intrauterine"[All Fields] AND "device"[All Fields]) OR "intrauterine device"[All Fields]) AND (Randomized Controlled Trial[ptyp] AND English[lang]).

This returned 1 study which was not eligible for inclusion the review.

A second survey was conducted without the randomized controlled trial filter and this retrieved 23 studies of which 1 study was found to be relevant to the aim of the review. An open, parallel group trial comparing the single-rod etonogestrel and two-rod levonorgestrel subdermal implants (randomized) and the copper IUCD with a surface area $\geq$ 375 mm^2 (non-randomized) was identified.

A POPLINE search was conducted using the key words contraceptive implants, levonorgestrel and Jadelle. This returned 13 studies, of which none were randomized controlled trials relevant to the outcomes of the review. The search identified a relevant review of the scientific data of Jadelle®. The review in turn identified 1 non-comparative study evaluating the contraceptive effectiveness and safety of Jadelle®.

A second POPLINE search was conducted using the key words contraceptive implants, etonogestrel and implanon. This returned 66 studies, of which none were randomized controlled trials relevant to the outcomes of the review.

A search of The Cochrane Database of Systematic Reviews identified 1 relevant review comparing the efficacy, tolerability and acceptability of subdermal implants *versus* other reversible contraceptive methods.

A National Institute for Health and Clinical Excellence (NICE) guideline (2005) on long-acting reversible contraception and an earlier Health Technology Assessment (HTA) review of subdermal implants and intrauterine systems *versus* other reversible contraceptive methods (conducted in 2000) were identified.

The systematic reviews and NICE guideline identified 1 additional study not identified from the literature surveys but considered to be eligible for inclusion in the review.

Evidence synthesis and quality:

Levonorgestrel (LNG) two-rod subdermal implant

Effectiveness

Pregnancy rate

The Cochrane review found no significant difference in pregnancy rate (no. of pregnancies/100 women years) between the two-rod LNG (Jadelle®) and 6-capsule LNG (Norplant®) implants during the 5 year study period (0.13 and 0.09/100 women years for Jadelle® and Norplant® respectively) on the basis of a single randomized controlled trial (this study is presented in table 1; refer to reference 7).[4]

Table 1: Summary of pregnancy rates for randomized, open-label, comparative studies evaluating the contraceptive effectiveness of the two-rod LNG subdermal implant

Study reference	Intervention/s (no. of patients)	Study follow-up (in years)	Description of participants	Number of pregnancies /100 women years for duration of follow-up period	Comments
5	LNG 2-rod implant Jadelle ® (600) LNG 6-capsule implant Norplant ® (598)	3	18-40 years Variable parity (<2 births on average)	0.0 0.0	Method of randomization and allocation concealment explained. Not known whether the analysis was intention to treat (ITT).
6	LNG 2-rod implant Jadelle ® (199) LNG 2-rod implant Norplant II ® (199)	3	18-40 years Variable parity (<2 births on average)	0.0 0.0	Method of randomization and allocation concealment explained. Not known whether the analysis was ITT.
7	LNG 2-rod implant (600) LNG 6-capsule implant (598)	5	18-40 years Variable parity (<2 births on average)	0.13 0.09 Annual pregnancy rate/ 100 women years	Method of randomization and allocation concealment explained. Not known whether

				At year 3: 0.0 and 0.0 At year 5: 1.0 and 0.7	analysis was ITT.

Although Jadelle® is registered for use for 5 years, the study conducted by Sivin and colleagues in 1998 (refer to table 1; reference 7) showed a change in the pregnancy rate from year 3 to year 5. A non-comparative trial reported a pregnancy rate of 0.4/100 women years at year 3 and no pregnancy occurring at year 5 (3 and 5-year cumulative pregnancy rate 0.8/women years).[8]

Other outcomes

Continuation rate

The Cochrane review reported no significant difference in the continuation rate (no. of pregnancies/100 women users) between the two-rod LNG (Jadelle®) and 6-capsule LNG (Norplant®) subdermal implants during the 5 year follow-up period (55.1 and 53.0/100 women users for Jadelle® and Norplant® respectively) on the basis of 1 study (refer to table 1; reference 7).[4] The 1997 study by Sivin and colleagues (refer to table 1; reference 5) reported similar continuation rates during the 3 year follow-up period (71.3 and 71.1/ 100 women years for Jadelle® and Norplant® respectively).

Safety

Menstrual disturbances

The Cochrane review reported no significant difference in the discontinuation rates (no. of pregnancies/100 women years) between the two-rod LNG (Jadelle®) and 6-capsule (Norplant®) subdermal implants due to menstrual problems during the 5 year study period (16.4 and 19.2/100 women years for Jadelle® and Norplant® respectively) on the basis of 1 study (refer to table 1; reference 7). Only 3 women in the LNG subdermal implant group discontinued the method as a result of amenorrhoea. Similarly, the 1997 study by Sivin and colleagues reported low discontinuations rates as a result of menstrual problems for the LNG subdermal implant during the 3 year follow-up period (11.4 and 12.2/100 women years for Jadelle® and Norplant® respectively). Only 2 women in the LNG subdermal implant group discontinued the method as a result of amenorrhoea.

ENG single-rod subdermal implant

Efficacy and effectiveness

Pregnancy rate

The Cochrane review reported that there were no pregnancies in either the single-rod ENG (Implanon®) or 6-capsule LNG (Norplant®) subdermal implant groups after the 4 year follow-up period. This finding was derived from 8 comparative clinical trials of Implanon® *versus* Norplant® (1578 participants, aged 18 – 40 years) conducted by the manufacturer during the development of Implanon® between 1989 to 1998.[4]

An earlier HTA reported a similar result on the basis of a meta-analysis conducted in 1998 evaluating the mechanism of action and efficacy of Implanon®.[9] The meta-analysis included 13 comparative and non comparative manufacturer sponsored clinical trials that met the requirements for good clinical practice, of which 6 were included in the Cochrane review for the analysis of pregnancy rate.[10]

In 2008/9 there were a 2 reviews published on the efficacy and/or safety of the ENG subdermal implant (Implanon®) using data captured from 11 comparative and non comparative manufacturer sponsored clinical trials (946 participants, age 18 – 40 years, 10 completed phase II and III studies and 1 completed phase IV study) from an international integrated clinical trial safety database. The results from these clinical trials supported the approval of the ENG subdermal implant by the United States Food and Drug Administration Similar to the Cochrane and HTA reviews, the 2008/9 reviews reported no pregnancies while the ENG subdermal implant was in place.[11] [12] Three of the comparative clinical trials in these reviews were included in both the Cochrane and HTA reviews previously discussed.

The NICE guideline concurred with the above mentioned reviews that no pregnancies were reported on the basis of the clinical trials conducted by the Implanon® manufacturer.[13] The NICE guideline also acknowledged reports of unintended pregnancies submitted to the Australian Adverse Drug Reactions Advisory Committee during post-marketing surveillance.[13] [14]

Other outcomes

Continuation rate

The Cochrane review found no significant difference in the continuation rates between the single-rod ENG (Implanon®) and 6-capsule LNG (Norplant®) subdermal implants during the 4 year follow-up period on the basis of the 8 clinical trials conducted by the Implanon® manufacturer.

Safety

Menstrual disturbances

The Cochrane review concluded no significant differences between the single-rod ENG (Implanon®) and 6-capsule LNG (Norplant®) subdermal implants for infrequent, frequent and prolonged bleeding for a 2 year follow-up period based on the available data from the 8 manufacturer sponsored clinical trials. Of the 8 clinical trials, only 1 reported data beyond 3 years. This study conducted by Zheng and colleagues (200 participants, age 20 – 35 years) showed no statistical difference in the percentage of women complaining of bleeding problems between the single-rod ENG and 6-capsule LNG subdermal implant groups, except at month 27 (19.8% vs. 5%, $p < .0.01$).[16]

LNG *versus* ENG subdermal implant OR LNG and/or ENG subdermal implant *versus* copper IUCD and/or levonorgestrel intrauterine system

A recent parallel-group trial (2981 participants, 18 – 45 years) by Meirik and colleagues presented data on outcomes related to the insertion of LNG, ENG subdermal implants (e.g. duration of implant insertion, complications at insertion, ease of insertion) and the copper IUCD with a surface area > 375mm^2 after a 6 week follow-up period.[15] Only the implant users were randomized. The method of randomization and allocation concealment was explained but the study was not blinded. The authors reported that there were no clinically relevant differences in the insertion outcomes after the 6 week follow-up period. The outcomes of relevance to this review *i.e.* the comparative effectiveness and safety of these contraceptive methods will only be examined in future publications.

Alternative agents:

- 380 mm² copper intrauterine contraceptive device.

Summary:

The evidence presented suggests that the two-rod LNG (Jadelle®) and single-rod ENG (Implanon®) subdermal implants are effective and safe long-term reversible contraceptive methods. This conclusion however must be carefully viewed against the limitations of the evidence identified and presented in this review. The available data of

the effectiveness and safety of Jadelle® is derived from a limited number of randomized controlled trials. The findings supporting the efficacy, effectiveness and safety of Implanon® is currently limited to clinical trials conducted by the manufacturer. The effectiveness and safety of the two-rod LNG subdermal implant *versus* the single-rod ENG subdermal implant or; the effectiveness of the two-rod LNG and/or single-rod ENG subdermal implant *versus* the copper IUCD with a surface are 375mm^2 is currently unknown.

Recommendation:

Given the paucity of comparative data on the effectiveness and safety of the two-rod LNG implant, single-rod ENG implant and copper IUCD > 375mm^2, the committee supports the current recommendation for copper IUCD > 375mm^2 in the Primary Health Care Standard Treatment Guidelines and Essential Medicines List. The inclusion of the two-rod LNG or single-rod ENG implant as an additional long-acting reversible contraceptive should be based on the availability and cost of these contraceptive methods.

Review indicators:

- Randomized controlled trials evaluating the effectiveness and safety of the single-rod ENG subdermal implant;
- Randomized controlled trials comparing the effectiveness and safety of the two-rod LNG and single-rod ENG subdermal implant and;
- Randomized controlled trials comparing the effectiveness and safety of the two-rod LNG and/or single-rod ENG implant *versus* copper IUCDs > 375mm^2.

References:

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