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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

ETONOGESTREL EXTENDED-RELEASE SUBDERMAL IMPLANT (NEXPLANON — MERCK CANADA INC.)
Indication: Prevention of pregnancy for up to three years.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that etonogestrel extended-release radiopaque subdermal implant should be reimbursed for the prevention of pregnancy for up to three years only if the following condition is met.

Condition for Reimbursement
Cost should not exceed the negotiated annualized cost of reimbursed comparable long-acting contraceptive options.

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that etonogestrel extended-release radiopaque subdermal implant should be reimbursed for the prevention of pregnancy for up to three years only if the following condition is met.

Condition for Reimbursement

Pricing Condition

1. Cost should not exceed the negotiated annualized cost of reimbursed comparable long-acting contraceptive options.

Reasons for the Recommendation

1. Data from two studies, Study P05702 (N = 301) and Study 34528, and an integrated analysis of 11 studies (N = 945) demonstrates that etonogestrel implant is effective in preventing pregnancies in healthy women with regular menstrual cycles. Women in these studies had a body mass index less than 35 kg/m^2 and were treated with the radiopaque or non-radiopaque etonogestrel implant for up to three years. There were no pregnancies during the treatment periods across all of the reviewed studies. Hence, the Overall Pearl Index was zero contraceptive failures per 100 woman-years (95% confidence interval [CI], 0 to 0.20) for the non-radiopaque etonogestrel implant in the integrated analysis during the treatment period, and zero contraceptive failures per 100 woman-years (95% CI, 0 to 0.56) for the radiopaque etonogestrel implant in Study P05702 (a user satisfaction study) during the treatment period plus 14 days. The Overall Pearl Index during the treatment period of bioequivalence Study 34528 was zero contraceptive failures per 100 woman-years (95% CI, 0 to 3.04) and zero contraceptive failures per 100 woman-years (95% CI, 0 to 3.06) in the radiopaque and non-radiopaque etonogestrel implant arms, respectively. Similar results were reported based on the Annual Pearl Index.
2. From a cost perspective, the average annual cost of using etonogestrel is less expensive than most forms of contraception, except for copper-releasing intrauterine devices (IUDs) and levonorgestrel-releasing intrauterine systems (IUSs) if used for the full three years.

Discussion Points

- CDEC noted the absence of direct and indirect comparisons of radiopaque etonogestrel implant to relevant contraceptives used in Canada. The pivotal studies included an integrated analysis pertaining to the non-radiopaque etonogestrel implant, and two studies on the radiopaque etonogestrel implant: P05702 (a non-comparative, single-arm, clinician satisfaction study) and 34528 (a double-blind, parallel-group, bioequivalence study). Based on evidence presented in these trials, CDEC noted that etonogestrel would have similar efficacy as currently reimbursed long-term contraceptives. However, it was noted that the lack of comparative data, especially for adverse events (AEs), was a major evidence gap associated with this product.
- The clinical trials included a homogeneous patient population and key characteristics such as age, race, and weight may limit the generalizability of the study findings to the Canadian population. The studies reviewed did not evaluate women under the age of 18 or over the age of 40, or those outside of the studied weight range. The majority of the those included in the trials were White. The decision to use etonogestrel or alternatives in populations outside those studied should be primarily a clinical decision in collaboration with the patient.
- CDEC discussed that bleeding-related AEs (including dysmenorrhea, menorrhagia, metrorrhagia, vaginal hemorrhage, and genital hemorrhage) occurred in 5.3% to 28.2% of patients treated with the radiopaque etonogestrel implant in Study P05702, as well as in 3.8% to 46.2% and 7.1% to 41.1% of patients treated with the radiopaque and non-radiopaque etonogestrel implant in Study 34528, respectively. In the integrated analysis, 13.6% of patients stopped treatment due to AEs, with the most common reason attributed to bleeding irregularities (11.1%). In Study P05702, 35.2% of patients treated with the radiopaque etonogestrel implant stopped treatment due to an AE, with bleeding irregularities accounting for 19.3% of the withdrawals. The percentages of patients who stopped treatment due to AEs were similar for those treated with the radiopaque (28.8%) and non-radiopaque

etonogestrel implant (30.4%) in Study 34528. CDEC heard clinical expert opinion that higher withdrawal rates with the etonogestrel implant, compared to IUD or oral contraception, are expected based on both published data and clinical experience.

- CDEC noted two possible complications with etonogestrel implant: migration of the implant from the site of initial insertion and difficulties with removal. CDEC acknowledged that the training of clinicians on the proper insertion and removal of the implant is important as inadequate training may negatively impact the overall safety profile of the etonogestrel extended-release subdermal implant.
- When assessing cost-effectiveness, the lack of comparative clinical evidence was the main area of uncertainty. The comparative efficacy and AE profiles of the different contraceptive methods have not been assessed using direct or indirect methods. At the submitted price, etonogestrel has a lower annual cost, if used for the full three years, than non–long-acting contraceptives, such as oral contraceptives. Given that the efficacy of etonogestrel will likely be at least equivalent to non–long-acting contraceptives (as efficacy does not depend on user compliance), CDEC noted that etonogestrel would be cost-effective relative to non–long-acting contraceptives. The annual cost of etonogestrel not exceeding that of currently reimbursed long-acting contraceptives would help to ensure that etonogestrel is a cost-effectiveness option.

Background

Etonogestrel extended-release subdermal implant has a Health Canada indication for the prevention of pregnancy. Etonogestrel is the biologically active metabolite of desogestrel, a progestagen widely used in oral contraceptives. This radiopaque implant is a long-acting hormonal contraceptive that contains 68 mg of etonogestrel. The Health Canada–approved dose is for a single implant that is inserted subdermally and can be left in place for three years. The non-radiopaque formulation of etonogestrel is not available for use in Canada.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review of sponsor-provided studies of etonogestrel and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in obstetrics and gynecology.

Summary of Patient Input

No patient input was received for this CADTH report.

Clinical Trials

Three sponsor-identified studies were assessed in the CADTH report: an integrated analysis (N = 946), Study P05702 (N = 301), and Study 34528 (N = 108).

The integrated analysis included pooled data from 11 studies that evaluated the non-radiopaque etonogestrel implant as the intervention in healthy adult women. The objective of the integrated analysis was to present efficacy and safety results from the clinical trials that supported the FDA filing for the approval of the non-radiopaque etonogestrel contraceptive implant. Study P05702 was an open label, non-comparative, single-arm, clinician satisfaction study of adult women treated with the radiopaque etonogestrel implant. The primary objective of Study P05702 was to evaluate the use of the "next generation" applicator and its instructions for proper insertion of the radiopaque etonogestrel implant. The applicator available for use in Canada is the same as the applicator used in Study P05702. Study 34528 was a double-blind, parallel-group, bioequivalence study where women were randomized in a 1:1 ratio for treatment with the radiopaque etonogestrel implant or the non-radiopaque etonogestrel implant. Patients included in the three studies were healthy women between 18 to 40 years of age with regularly occurring menstrual cycles. Contraceptive efficacy was assessed in all three studies. The primary end point was user satisfaction in Study P05702 and bioequivalence in Study 34528. Each study lasted up to three years.

Key limitations across all studies included concerns about generalizability (as the study participants were a selective group when compared to all women of child-bearing age who could potentially receive etonogestrel) and high discontinuation rates (often related to bleeding irregularities). The generalizability of the study findings to clinical practice settings in Canada was limited by eligibility requirements that excluded certain patients, including adolescents, patients over the age of 40, patients with irregular menstrual

cycles, and patients with a body mass index greater than 35 kg/m^2. Evidence gaps include an absence of direct and indirect comparisons to relevant contraceptives used in Canada, and the efficacy of the radiopaque etonogestrel implant in subgroups of patients that were excluded in the trials. One of the major limitations of the three pivotal studies relates to the high number of discontinuations that occurred, as 34.9% to 48.2% of patients discontinued the trials over the three-year period. The substantial number of discontinuations raises questions about the validity, interpretation, and actual utility of the radiopaque etonogestrel implant in the clinical setting. It is unclear if the clinical efficacy of non-radiopaque etonogestrel would be the same for the patients who discontinued the trial compared with those who completed the trial. Theoretically, the three-year duration of the trials was sufficient to determine effectiveness for patients; however, the extensive number of discontinuations should be considered when assessing the actual treatment time. Many patients discontinued the trials in year 1 and year 2, and some of the included trials in the integrated analysis were only two years in duration; therefore, the totality of evidence is limited in assessing actual etonogestrel implant use at three years.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed contraceptive efficacy, return of menses to normal, palpability of the implant, X-ray visibility of the implant, time for insertion and removal, user satisfaction, and bioequivalence. The primary outcome in one study (integrated analysis) was contraceptive efficacy. User satisfaction (with the radiopaque etonogestrel implant) was assessed as the primary end point in one trial (Study P050702). The primary outcome in one trial (Study 34528) was bioequivalence between the radiopaque and non-radiopaque implant.

- Contraceptive efficacy was assessed using the Pearl Index, which calculates the failure rate for a contraceptive method per 100 women-years by dividing the number of unplanned pregnancies (numerator) by the number of months or years of exposure to the risk (denominator). The smaller the Pearl Index, the more effective the contraceptive method. The studies assessed the Overall Pearl Index (which counts pregnancies during the period of after implant insertion and before removal), and the Annual Pearl Index (which counts pregnancies per year of exposure). The Pearl Index is the most commonly reported measure of contraceptive failure in clinical studies; however, is not widely used in clinical practice.
- Return of menses to normal (Yes/No) was assessed three months after implant removal for women who were not pregnant, were not breastfeeding, and were not using post-treatment hormonal contraceptives, where "normal" was defined as the pre-treatment menses pattern.
- Palpability of the implant was assessed as palpable or not palpable.
- X-ray visibility of the implant was assessed as clearly visible or unclearly/not visible.
- The time for insertion and time for removal of the implant were assessed.
- User satisfaction (with the radiopaque etonogestrel implant) was assessed as the primary end point in Study P050702. The user satisfaction questionnaire was created specifically to evaluate investigator-reported satisfaction with the technical, design, function, and safety features of the applicator, as well as their satisfaction with the total time it takes to perform the insertion, and their overall impression of the applicator. The questionnaire consists of five overall questions, with sub-items for selected questions, and five possible answers ranging from very satisfied to very dissatisfied. No evidence on the validation, reliability, and responsiveness of the user satisfaction questionnaire was identified in the literature.
- Bioequivalence was determined using the following end points, which are consistent with guidance from Health Canada relating to comparative bioavailability standards:[27] peak etonogestrel concentration (C_{max}) and area under the curve (AUC) for etonogestrel at 6, 24, and 36 months (AUC_{6mo}, AUC_{24mo}, and AUC_{36mo}, respectively) after insertion assessed via blood sampling. Bioequivalence was defined as the 90% CI of the ratio radiopaque implant or non-radiopaque implant of the geometric means (GMR) within the acceptance range of 0.80 to 1.25.
- Health-related quality of life (HRQoL) outcomes were not evaluated in the reviewed studies.
- Harms were assessed as the occurrence of AEs, serious adverse events (SAEs), withdrawals due to AEs, deaths, and notable harms (e.g., bleeding irregularities).

Efficacy

Across all three studies zero pregnancies occurred during the treatment periods. The Overall Pearl Index was zero contraceptive failures per 100 woman-years (95% CI, 0 to 0.20) for the non-radiopaque etonogestrel implant in the integrated analysis during the treatment period and zero contraceptive failures per 100 woman-years (95% CI, 0 to 0.56) for the radiopaque etonogestrel implant in P05702 (user satisfaction study) during the treatment period plus 14 days. The Overall Pearl Index during the treatment period of bioequivalence Study 34528 was zero contraceptive failures per 100 woman-years (95% CI, 0 to 3.04) and zero contraceptive failures per 100 woman-years (95% CI, 0 to 3.06) in the radiopaque etonogestrel implant arm and non-radiopaque etonogestrel implant arm, respectively. Similar results were reported based on the Annual Pearl Index.

Based on findings from Study 34528, the radiopaque and non-radiopaque formulations were bioequivalent with respect to the GMR of: C_{max} (GMR = 1.06; 90% CI, 0.91 to 1.23); AUC_{6mo} (GMR = 1.00; 90% CI, 0.91 to 1.10); AUC_{24mo} (GMR = 0.98; 90% CI, 0.88 to 1.10), and AUC_{36mo} (GMR = 1.00; 90% CI, 0.89 to 1.11).

Return of menses to normal (pre-trial) pattern occurred for 83.5% of patients treated with the radiopaque etonogestrel implant in Study P05702. In Study 34528, 94.4% of patients treated with the radiopaque etonogestrel implant and 90.5% of patients treated with the non-radiopaque etonogestrel implant experienced return of menses to normal (pre-trial) pattern. This outcome was assessed three months after implant removal for women who were not pregnant, were not breastfeeding, and were not using post-treatment hormonal contraceptives. Return of menses to normal pattern was not assessed in the integrated analysis.

Palpability and X-ray visibility of the implant was assessed in studies P05702 and 34528. The radiopaque and non-radiopaque etonogestrel implants were palpable in almost all patients (97.1% to 100%) when assessed at various time points. The radiopaque etonogestrel implant was clearly visible in almost all patients (96.2% to 100%) after insertion and before removal. The product monograph includes a black box serious warning stating that at any time the implant is not palpable by the health care professional or the patient, the implant should be localized as soon as possible and removed as soon as medically appropriate to manage the risks of migration.[8] Implant migration was not assessed in the integrated analysis or Study 34528; however, one patient treated with the radiopaque etonogestrel implant in Study P05702 experienced an implant migration. The limited data from the pivotal trials on implant migration associated with the radiopaque etonogestrel implant is an important limitation. Findings from post-marketing reports of implants located within the vessels of the arm and the pulmonary artery were suspected to be attributed to deep insertions or intravascular insertion.[8] Real-world evidence has demonstrated implant migration of the radiopaque etonogestrel implant into pulmonary vasculature with an estimated incidence of 3.17 per 100,000 implants (95% CI, 1.37 to 6.24) based on 2017 data from a study in France.[9] While implant migration may be rare, it can lead to respiratory issues and life-threating conditions and highlights the importance of proper insertion by trained clinicians.

In the integrated analysis, the mean insertion time for the non-radiopaque etonogestrel implant was 78 seconds (standard deviation [SD] = 114.0), and the mean removal time was 228 seconds (SD = 294.0). In Study P05702, the mean insertion time for the radiopaque etonogestrel implant was 27.9 seconds (SD = 29.3), and the mean removal time was 119.3 seconds (SD = 120.2). The mean insertion time for the radiopaque etonogestrel implant in Study 34528 was 87.6 seconds (SD = 96.0) and 299.4 seconds (SD = 207.0) for removal. The insertion time for the non-radiopaque etonogestrel implant was 72.6 seconds (SD = 63.6) and the removal time was 264.6 seconds (SD = 241.8). Data from Study P05702 reported that the most common reason for complications during implant removal was attributed to the presence of fibrotic tissue around the implant (4.4%).

The frequency results for the user satisfaction questionnaire were assessed as the primary efficacy end point in the applicator user group (investigators) in Study P05702. Generally, as users completed more insertions, more users reported being “very satisfied” and fewer users reported being “very dissatisfied,” “dissatisfied,” and “not satisfied nor dissatisfied” based on assessments for design and technical aspects, functionality, safety, used time, and applicator satisfaction. The expected and actual treatment satisfaction for patients treated with the radiopaque etonogestrel implant were assessed in Study P05702. However, aggregate efficacy results were not available and could not be assessed for this review.

HRQoL, an important outcome to patients, was not evaluated in the pivotal studies.

Harms (Safety)

AEs were experienced by almost all patients (90.4% to 100.0% based on data from studies P05702 and 34528). Total AEs are a key harms measure and were not reported in the integrated analysis.

Bleeding irregularities were identified by the clinical expert consulted for the review as harms that were important to patients. When examined collectively, bleeding irregularities were the greatest source of AEs across the trials; however, an aggregate measure of AEs related to bleeding irregularities were not reported in any of the studies. The severity of bleeding (mild, moderate, or severe) was also not reported. Specific bleeding-related AEs (including dysmenorrhea, menorrhagia, metrorrhagia, vaginal hemorrhage, and genital hemorrhage) occurred in 5.3% to 28.2% of patients treated with the radiopaque etonogestrel implant in Study P05702, as well as in 3.8% to 46.2% and 7.1% to 41.1% of patients treated with the radiopaque and non-radiopaque etonogestrel implant in Study 34528, respectfully. In a subset of 780 patients (82%) at two years, specific bleeding irregularities (including amenorrhoea; and infrequent, frequent, and/or prolonged bleeding) occurred in 6.7% to 33.6% of patients.

In the integrated analysis, SAEs occurred in 5.9% of patients treated with the non-radiopaque etonogestrel implant. In Study P05702, 5.3% of patients treated with the radiopaque etonogestrel implant experienced an SAE. SAEs occurred similarly for patients treated with the radiopaque (7.7%) and non-radiopaque etonogestrel implant (10.7%) in Study 34528. None of the patients in studies P05702 or 34528 experienced SAEs related to bleeding; however, one patient per arm in Study 34528 experienced an SAE related to deep vein thrombosis. In the integrated analysis, one patient experienced an SAE related to the category “platelet, bleeding and clotting disorder.”

In the integrated analysis 13.6% of patients stopped treatment due to AEs, with the most common reason attributed to bleeding irregularities (11.1%). In Study P05702, 35.2% of patients treated with the radiopaque etonogestrel implant stopped treatment due to an AE, with bleeding irregularities accounting for 19.3% of the withdrawals. The percentages of patients who stopped treatment due to AEs were similar for those treated with the radiopaque (28.8%) and non-radiopaque etonogestrel implant (30.4%) in Study 34528. Bleeding irregularities accounted for 19.2% of patients treated with the radiopaque etonogestrel implant and 14.3% of patients treated with the non-radiopaque etonogestrel implant. There was one report of “mild” implant migration.

Indirect Treatment Comparisons

No indirect evidence was submitted by the sponsor. An independent literature search for indirect evidence conducted by CADTH did not identify any evidence that met the inclusion criteria of the CADTH review protocol.

Cost and Cost-Effectiveness

Etonogestrel is available as a radiopaque subdermal implant containing 68 mg of etonogestrel, at a submitted price of $285 per implant. If the implant is used for the full three years, the average daily and annual drug costs for etonogestrel are $0.26 and $95, respectively.

The sponsor submitted a cost-utility analysis from the perspective of a Canadian publicly funded health care payer over a three-year time horizon comparing etonogestrel to other long- and short-term, reversible, female-based contraceptives, including levonorgestrel-releasing IUSs, copper-releasing IUDs, oral contraceptive pills, the transdermal patch, and the vaginal ring. A multi-state Markov cohort model was developed using a 28-day cycle length. Individuals started in the model by initiating treatment with one of the contraceptive options and over time either continued using their current contraception; discontinued their contraception (switched to another form of contraception or stopped using contraception); or, became pregnant. The likelihood of becoming pregnant or discontinuing was taken from a single non-systematic review. Five pregnancy outcomes were considered, which were used to determine disutility, pregnancy costs, and time spent in the “pregnant” health state. To estimate HRQoL outcomes in the model, the sponsor assumed that individuals who become pregnant will experience a disutility associated with an unintended pregnancy (UIP). In addition, it was assumed that each of the pregnancy outcomes would have an additional associated disutility. AEs included in a published economic evaluation were selected for inclusion, with associated costs and disutilities. Other costs in the model included treatment acquisition costs, visits to physicians for contraceptive and pregnancy care, and a one-time cost associated with all pregnancy outcomes.

CADTH identified several key limitations with the sponsor's economic submission:

- There was a lack of comparative clinical efficacy and AE data provided by the sponsor, making it difficult to draw conclusions regarding comparative efficacy and harms between the contraceptive options considered in the model.
- There was a lack of appropriate data to determine what contraceptive method would be used in the second line if individuals discontinued their first-line method.
- The number of individuals who stop using contraceptive methods in the model was based on a function of method-specific discontinuation rates, which is inappropriate as the proportion of individuals who stop using contraceptives will likely be independent of contraceptives used.
- The disutility associated with an UIP lasted for one year, rather than the duration of the pregnancy.
- Copper IUD pricing reflected the cost of a three-year copper IUD, despite the five-year copper IUD being most commonly used by individuals in Canada.
- Abortion costs were overestimated, which resulted in increased costs associated with UIP.

CADTH was unable to address limitations associated with uncertain comparative clinical efficacy, discontinuation rates, and assumptions regarding contraceptive switching. Given significant uncertainty for these parameter values, CADTH was unable to establish a base case for the cost-effectiveness of etonogestrel versus IUS. However, CADTH concluded that if it is believed that etonogestrel is as clinically effective and safe as other contraceptive alternatives, then it could represent a cost-effective use of health care resources.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Ms. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

September 15, 2020 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

None