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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

ETONOGESTREL EXTENDED-RELEASE SUBDERMAL IMPLANT (NEXPLANON)

Merck Canada Inc.

Indication: For the Prevention of Pregnancy

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
BIA	budget impact analysis
CIHI	Canadian Institute for Health Information
ICER	incremental cost-effectiveness ratio
IUD	intrauterine device
IUS	intrauterine system
QALY	quality-adjusted life-year
UIP	unintended pregnancy
UTI	urinary tract infection
VAS	visual analogue scale
VTE	venous thromboembolism

Executive Summary

The executive summary is comprised of two tables (Table 1: Background and Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Etonogestrel 68 mg extended-release subdermal implant (Nexplanon)
Submitted price	Etonogestrel, 68 mg implant, $285
Indication	For the prevention of pregnancy up to 3 years
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	May 25, 2020
Reimbursement request	As per indication
Sponsor	Merck Canada Inc.
Submission history	Previously reviewed: Reviewed and withdrawn prior to CDEC meeting. New submission includes a budget impact analysis

CDEC = CADTH Canadian Drug Expert Committee; NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Females of reproductive age (15 to 49 years) at risk of becoming pregnant
Treatment	Etonogestrel
Comparator(s)	Long- and short-term female-based reversible contraceptive methods: • Hormonal intrauterine system (IUS) • Copper intrauterine device (IUD) • Injectable progestin • Oral contraception • Contraceptive patch • Vaginal ring
Perspective	Canadian publicly funded health care payer
Outcome	Quality-adjusted life-years (QALYs)
Time horizon	3 years
Key data source	Trussell
Submitted results for base case	ICER = $9,121 per QALY, for etonogestrel compared to the copper IUD. All other comparators were dominated
Key limitations	• Lack of appropriate comparative clinical efficacy and adverse data provided by the sponsor • Lack of appropriate data to determine which contraceptive method would be used as a second-line option if individuals discontinued their first-line method • The number of individuals who stop using contraceptive methods considered in the model is 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 • Disutility associated with an unintended pregnancy (UIP) lasts for 1 year, rather than the duration of the pregnancy • Copper IUD pricing reflected the cost of a 3-year copper IUD, despite the 5-year copper IUD being most commonly used by individuals in Canada • Costs of abortion were overestimated, which resulted in increased costs associated with UIP
CADTH reanalysis results	CADTH reanalyses included applying a constant dropout rate across contraceptives and removing pregnancies from dropouts from the analysis, adjusting the disutility for a UIP by the average time spent pregnant in the model, using the price of a 5-year copper IUD, assuming individuals will not discontinue after the 3-year model time horizon, adjusting the cost of abortion to reflect the outpatient nature of the procedure and removing fixed costs from the probabilistic analysis. • CADTH base case ICER = $1,251 per QALY for etonogestrel compared to the copper IUD. All other comparators were dominated CADTH was unable to address limitations associated with uncertain comparative clinical efficacy, discontinuation rates, and assumptions regarding contraceptive switching. Results are contingent on the interpretation of the clinical evidence (see CADTH scenario analyses explored). If it is believed that etonogestrel is as effective and safe as other contraceptive alternatives, then it represents a cost-effective use of health care resources.

ICER = incremental cost-effectiveness ratio; IUD = intrauterine device; IUS = intrauterine system; QALY= quality-adjusted life-year; UIP = unintended pregnancy.

Conclusions

The CADTH reanalysis showed that etonogestrel is expected to cost $7 more but yield 0.006 fewer quality-adjusted life-year (QALY) losses than the copper intrauterine device (IUD), leading to an incremental cost-effectiveness ratio (ICER) of $1,251 per QALY. It was shown to be at least as effective and less costly than all other contraceptive options considered. The model lacked robust evidence for key aspects which limited CADTH's ability to derive a reliable base-case estimate. Instead, in CADTH reanalyses, key parameters, such as efficacy, are based on assumptions.

From a cost perspective, the annual cost of using etonogestrel is less expensive than most forms of contraception, except for copper IUDs and intrauterine systems (IUSs) if used for the full three years. The lack of comparative evidence is the main limiting factor as the efficacy and adverse event (AE) profiles of the different contraceptive methods have not been addressed in any way using direct or indirect methods. Although etonogestrel appears economically attractive, this result is grounded in assumptions of comparative effectiveness with other contraceptive methods, mainly IUSs. If it is believed that etonogestrel is as effective and safe as other contraceptive alternatives, then it represents a cost-effective use of health care resources.

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Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

No input was received.

Economic Review

The current review is for etonogestrel (Nexplanon) for females of reproductive age (15 to 49 years) at risk of becoming pregnant.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis comparing etonogestrel to other short and long-term female-based reversible contraceptive methods available in Canada for the prevention of pregnancy in women of reproductive age (15 to 49 years), which is aligned with the Health Canada indication.[1] Etonogestrel is available as a radiopaque subdermal implant containing 68 mg of etonogestrel, which is released at a rate of approximately 35 mcg to 45 mcg daily for the first year, 30 mcg to 40 mcg daily for the second year, and 25 mcg to 30 mcg daily at the end of the third year.[1] At the sponsor's submitted price of $285 per implant, the average annual cost is $95 per individual (or $0.26 daily), if the implant is used for the full three years.[2] Etonogestrel should be administered by health care professional who has received training and instruction on insertion and removal. The implant can be left in place for three years but may be removed at any time after insertion.

Comparators included short-term hormonal options, including oral contraceptives, the transdermal patch, and the vaginal ring. Also included were long-term hormonal options (levonorgestrel-releasing IUSs) and non-hormonal options (copper-T IUDs). Patients may switch from their initial contraception to an alternative contraceptive should they discontinue or become pregnant. The probability of switching to a given contraceptive was based on the market shares of the remaining contraceptive options.

The outcomes estimated in the economic evaluation were QALYs, number of unintended pregnancies (UIPs), and total costs. The economic analysis was conducted over a seven-year time horizon from the perspective of a publicly funded health care payer. An annual discount of 1.5% per year was applied to both costs and outcomes.

Model Structure

A cohort Markov model using 28-day cycle lengths (13 cycles per year) was submitted by the sponsor (see Figure 1). All individuals started in the "original" health state, where they initiated contraception using one of the included methods. In each cycle, individuals could remain on their original contraception, and thus in the original health state. Alternatively, individuals could transition to a "switch" state, where they switched contraceptive methods based on market shares of remaining contraceptive options (Table 13) or a "dropout state," in which they stopped using contraception for reasons including planning to get pregnant. Finally, from the original health state, individuals may also transition to the "pregnant" state. From the switch and dropout event states, individuals can either remain in these states or transition to the pregnant state. The model looks at five pregnancy outcomes associated with the pregnant state: birth with Caesarean section, birth with vaginal delivery, miscarriage or fetal loss, induced abortion, or ectopic pregnancy.[2] Pregnancy outcomes were used to determine disutility, prenatal care visit frequency, pregnancy outcome costs, and the time spent in the pregnant state (four cycles for miscarriage, induced abortion, or ectopic pregnancy, and 10 cycles for birth).

From the pregnant state, individuals transition to the “post-partum” state for one cycle, where they remain off contraception and are not at risk of pregnancy. From the post-partum state, individuals transition to the “prior pregnant” state, in which they initiate a contraceptive method based on market shares of all comparators. Individuals can remain in the prior pregnant state or transition to the pregnant state.

Model Inputs

The probabilities of becoming pregnant and discontinuing a contraceptive were derived from Trussell (Table 12).[3] Trussell provided an overview of contraceptive failure and discontinuation rates in the US by looking at observational data, using the National Survey of Family Growth for oral contraceptives, transdermal patches, vaginal rings, and injectable progestin.[4,5] Data from Sivin was used to inform rates for the copper IUD.[6] A weighted average of three studies was used to inform rates for the IUS.[7,8,9] For etonogestrel, Trussell arbitrarily set the failure rate to 0.05%. This approach was taken because the clinical trials reviewed by Trussell found zero pregnancies; however, pregnancies with etonogestrel have been reported from post-marketing surveillance data of Implanon.[3,10] Probabilities of the pregnancy outcomes were stratified by age group and were independent of contraceptive method.

Discontinuation for etonogestrel was based on the 1995 National Survey of Family Growth and was assumed to be equal to Norplant (Table 12). Of those who discontinue, the sponsor assumed 90% will switch contraceptive methods and 10% will drop out or cease using methods considered in this analysis. Individuals who drop out could become pregnant based on Canadian age-specific fertility rates.[11] The model included contraceptive-specific AEs, including venous thromboembolism (VTE), amenorrhea, and urinary tract infection (UTI), with AEs and rates being identified from a 2009 cost-effectiveness study.[12]

To estimate health-related quality of life outcomes in the model, the sponsor assumed that individuals who become pregnant will experience a disutility associated with a UIP (Table 14). The disutility associated with UIP was based on a US study that estimated utility using a visual analogue scale (VAS).[13] The disutility of a UIP was assumed to last for a year. It was assumed that the pregnancy outcomes would have an additional disutility, which were sourced from a US study of costs and health benefits that elicited utility values for pregnancy outcomes using the time trade-off technique (Table 14).[14] UTI and VTE AEs had an associated disutility, with values being sourced from a study on health-related quality of life and a previous cost-effectiveness study, respectively.[15,16]

Costs in the model included acquisition costs for contraceptives that were sourced from DeltaPA.[17] For contraceptive methods for which more than one product exists (i.e., IUS, copper IUD, and oral contraceptives), the sponsor took a weighted average of the costs using market shares of all brands and generics available. Health care resource use costs included visits to family physicians and gynecologists for contraceptive care.[2] Costs associated with pregnancy included the costs of prenatal care visits. It was assumed that all pregnancy outcomes aside from birth would have three prenatal care visits, and both birth outcomes would have 13 prenatal visits, based on Society of Obstetricians and Gynaecologists of Canada recommendations.[18] All pregnancy outcomes are associated with one-time costs, with costs of birth outcomes being sourced from Canadian costing sources.[19-21] Other costs included those related to contraceptive care (i.e., device insertion and removal) and AE costs for UTI and VTE.

Summary of Sponsor's Economic Evaluation Results

The sponsor presented probabilistic analyses (5,000 iterations).

Base-Case Results

The sponsor found that, compared with the copper IUD, etonogestrel was $77.67 more expensive and yielded 0.01 fewer QALY losses, resulting in an incremental cost-effectiveness ratio of $9,121 compared with the copper IUD (Table 3). A breakdown of UIP-related QALY losses and costs are provided in Table 11. All other comparators were dominated (i.e., more expensive and less effective).

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Copper IUD	691	–0.02	
Etonogestrel	768	–0.01	$9,121
Dominated treatments			
IUS	904	–0.02	Dominated
Injectable progestin	1,580	–0.06	Dominated
Oral contraceptive	1,773	–0.07	Dominated
Contraceptive patch	1,994	–0.08	Dominated
Vaginal ring	2,063	–0.08	Dominated

ICER = incremental cost-effectiveness ratio; IUD = intrauterine device; IUS = intrauterine system; QALYs = quality-adjusted life-years.

Note: Only treatments that are on the efficiency frontier are reported in the main body. Full results are reported in Appendix 3. Results were calculated based on the sponsor's results and reported per individual.

Source: Adapted from sponsor's pharmacoeconomic submission.[2]

Sensitivity and Scenario Analysis Results

Scenario analyses on the base case were performed by the sponsor by applying different discount rates, setting discontinuation rates to 0%, examining a broader society perspective and not including AEs in the analysis. Results of the sponsor's sensitivity analysis demonstrated that the model was robust to discontinuation rates. In the 0% discontinuation scenario which also adjusted the price of IUSs to reflect the time horizon, the ICER for etonogestrel compared to the copper IUD increased to $12,692 per QALY gained. In the societal perspective scenario, the ICER for etonogestrel decreased to $3,360 per QALY gained, compared to the copper IUD.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Appropriate comparative efficacy data are lacking.** Typical use contraceptive failure rates and one-year discontinuation rates were obtained primarily from a review article by Trussell.[3] Several concerns exist regarding the choice and reliability of the comparative efficacy data. First, the Trussell study provides a narrative overview, rather than a systematic review or meta-analysis of contraceptive efficacy. Not conducting a systematic review introduces bias to the studies selected, and given that the included studies were conducted in different populations with potentially different baseline characteristics, interpretation of comparative efficacy among contraceptive methods is limited. Importantly, the data used to populate efficacy failure rates for etonogestrel were

based on a failure rate that was set arbitrarily by Trussell and discontinuation data were based on a different implant product. This evidence was not reviewed as part of the clinical review report as observational data were not captured by the clinical protocol.

The sponsor did not provide direct or indirect comparative evidence between etonogestrel and other relevant contraceptives used in Canada. The absence of this data makes it difficult to draw concrete conclusions regarding comparative efficacy between the contraceptive options considered in the model.

- Given the uncertainty regarding comparative efficacy between etonogestrel and other long-acting reversible contraceptives, the influence of contraceptive failure and discontinuation rates will be explored in sensitivity analyses by assuming equal efficacy and discontinuation for etonogestrel and IUS.

- **There is uncertainty in the AEs selected.** The evidence used to populate AE rates in the model is uncertain. The AE rates were sourced from a 2009 study by Trussell examining the cost-effectiveness of contraceptives in the US.[12] The sponsor selected the same AEs and used the same rates as those used in this study when populating the cost-utility analysis. However, the original study itself gave no justification for why certain AEs were chosen and why certain studies were used to populate the rates; therefore, it is unclear why AEs of interest were chosen for this economic analysis. According to the clinical expert consulted for this review, thromboembolic disorders, depression, and mood disorders may be important AEs of interest for etonogestrel. Additionally, justification regarding how studies were selected to populate AE rates in the 2009 cost-effectiveness study was not provided. The sponsor assumed that individuals who received etonogestrel would not experience VTEs; however, two individuals in Study 34528 (a bioequivalence study) experienced a deep vein thrombosis, although the absence of a control makes interpretation of this finding difficult. Both the sponsor's integrated analysis and Study 34528 did not assess implant migration, which the CADTH clinical review report notes to be an important limitation.[22,23] However, there have been post-marketing reports of implant migration, an AE that was not included in the sponsor's pharmacoeconomic analysis.[1] Overall, the selection of AEs to include in the analysis was inadequately justified and an absence of direct and indirect comparisons of harms data prevents strong conclusions from being made about the comparative safety of etonogestrel with other contraceptives used in Canada.

  - Given the uncertainty regarding AE rates used in the model, CADTH explored the influence of setting the frequency of VTEs for etonogestrel as equal to that of oral contraceptives in a scenario analysis.

- **Contraceptive switching and contraceptive choice post-pregnancy are independent of an individual's previous contraception method.** In every model cycle, individuals may discontinue their current contraceptive class and switch to another contraceptive class included in the analysis. There is no option for individuals to switch to a different contraceptive option within the same class. The likelihood of individuals switching to a given contraceptive is based on the market shares of the remaining contraceptive class options.[2] The contraceptive individuals use after a UIP is determined by the market share of all contraceptives, including the contraceptive used when becoming pregnant. Market shares used in the sponsor's submission are provided in Table 13. According to the clinical expert consulted for this review, these market share estimates are not reflective of the Canadian clinical context as more individuals are on oral contraceptives and fewer are using copper IUDs or an IUS.

  The choice of contraception after switching has a large influence on the overall costs and QALYs given the large number of people who discontinue from their original contraceptive method. For example, as etonogestrel has a market share of 10% and IUS has a market share of 48%, individuals who discontinue etonogestrel have a high chance of switching to IUS, which has a low contraceptive failure rate. However, if an individual is using IUS and switches, because the market share of IUS is high, they are more likely

than etonogestrel individuals to switch to a less effective contraceptive method, resulting in higher total UIPs in individuals who start on an IUS.

In addition, the use of market shares to determine contraceptive use after discontinuing or becoming pregnant has limited validity as it assumes that the contraceptive method that individuals switch to is independent of their original method. According to the clinical expert consulted for this review, subsequent contraceptive use after discontinuation or UIP is unlikely to be independent of the original method. Rather, the choice of contraception is likely to be related to the reason for discontinuing, such as side effects or ease of use.

- Given the lack of validity in the approach of using market shares to determine subsequent contraceptive use, CADTH explored the influence of market shares in scenario analyses.

- **Dropout rates are a function of method-specific discontinuation rates.** In the sponsor's base case, a dropout state was included to account for individuals who were either no longer using contraception on the basis of either planning on becoming pregnant or switching to a method that was not included in the analysis, such as condoms. Dropouts were calculated by assuming 10% of discontinuations will drop out. The higher the discontinuation rate for a given contraceptive, the higher the proportion of individuals who drop out. According to the clinical expert consulted for this review, an individual's desire to become pregnant is likely not influenced by their current contraception, hence contraception-specific dropout rates have limited validity. Individuals in the dropout state may become pregnant according to Canadian age-specific fertility rates, meaning methods with higher discontinuation rates will result in more pregnancies. Additionally, although dropouts may occur because individuals are planning a pregnancy, pregnancies occurring in individuals who have dropped out have the same QALY loss associated with a UIP due to contraceptive failure.
  - To address the issue regarding dropouts being a function of discontinuation rates, the assumption that 10% of individuals who discontinue dropout was removed from the CADTH reanalyses. Instead, a constant dropout rate of 6% over three years across all age-cohorts and for all contraceptive methods was assumed based on data sent by the sponsor in response to a request made by CADTH for additional information.[24] These data from the sponsor's integrated analysis demonstrated that approximately 6% of individuals discontinued etonogestrel due to planning to become pregnant. As the same rate is applied to all contraceptive options the impact of UIPs from individuals who drop out does not influence the model's results.
- **Uncertainty exists in the discontinuation rates after the first year of contraception use.** In the sponsor's model, method-specific discontinuation rates in the first year were derived by calculating a yearly discontinuation rate from one-year continuation rates from Trussell.[3] In subsequent years, the sponsor assumed that discontinuation is reduced by 25% compared to the previous year. According to the clinical expert consulted for this review, the validity of this assumption is uncertain. Likewise, discontinuation rates were not obtained from the same population and no adjustments were made to address this issue, meaning that comparing discontinuation rates across comparators is uncertain.
  - CADTH addressed uncertainty in the discontinuation rates in scenario analyses by setting discontinuation for etonogestrel equal to IUS, and by setting discontinuation to 0% in years 2 and 3 for all comparators.
- **An incorrect approach was used to implement the disutility associated with a UIP.** The sponsor assumed that individuals experiencing a UIP would have an associated disutility of 0.32,[2] based on an American study of women presenting at pregnancy testing clinics that used several approaches to measure utility in a variety of pregnancy contexts (e.g., intention and planning of pregnancy).[13] The study authors concluded that of the four measures of quality of life used, only the VAS reflected a difference in quality

of life between different pregnancy contexts (i.e., those who were planning pregnancy compared to those who had a UIP). Therefore, the value derived from this method was used by the sponsor.[2,13] This approach is limited for several reasons. First, using a disutility of 0.32 assumes that, had the individual not experienced a UIP, their utility value would be equal to one, or perfect health. As the general female population utility in this age group may range from 0.862 to 0.902, the influence of a UIP on one's overall utility is likely to be the difference between their average utility and the utility experienced when receiving a diagnosis of a UIP (0.222 to 0.182).[25] In the same study, women who were happy with pregnancy news had a utility of 0.88.[13] Therefore, the assumption that individuals would be experiencing perfect health had they not had a UIP is limited.

Second, the VAS is a direct method of eliciting health state valuations. According to CADTH guidelines for economic evaluations, it is preferable to use health preferences obtained by an indirect method of measurement.[26] Third, the disutility value associated with a UIP is highly uncertain. The study used by the sponsor found that utility scores varied significantly depending upon the method of elicitation, with values ranging from 0.68 to 0.9996 for individuals who did not intend on getting pregnant.[13] The inability of the standard gamble and time-trade-off measures to detect large differences in utility may not mean that these measures are inappropriate, but rather that individuals experiencing a UIP may not be willing to accept a risk of death or a trade-off of time at the end of their life to avoid the UIP.[13] Disutility values from other sources identified by the sponsor also varied greatly, ranging from 0.0375 from a study using the time-trade-off technique to 0.513 in a study using the VAS.[14,27]

A further limitation of the disutility approach was identified regarding how disutility was implemented in the analysis. Disutility was used in the QALY estimation by multiplying the total number of pregnancies in each year by 0.32. This approach assumes that the disutility experienced by individuals with UIP lasts for a year. Justification for this assumption was not provided by the sponsor. The length of time that the disutility of a UIP occurs for is highly uncertain and depends on various assumptions.

In addition to the disutility associated with a UIP, individuals also experience a disutility associated with all pregnancy outcomes. These values were estimated using a time-trade-off technique and were applied additively to the disutility of the UIP.[14] It is unclear from the study regarding the length of time the disutility of these outcomes lasts for and, therefore, how they would be applied to generate QALY estimates.[14] Additionally, the appropriateness of adding further disutility associated with a pregnancy outcome on top of the disutility of a UIP requires a variety of assumptions. By adding the disutility associated with pregnancy outcomes to the general disutility associated with a UIP, it is assumed that there is no over-lapping disutility between the two outcomes. As this is unlikely to be the case and, this approach will likely double-count some disutility associated with UIPs.

- In the CADTH reanalyses, it was assumed that the disutility of a UIP would occur for the duration of time spent pregnant (i.e., nine months for individuals who give birth and four months for those with other birth outcomes, as per the sponsor's assumptions).
- As the disutility value associated with a UIP is uncertain, using the disutility value for a UIP from Lundsberg was explored in a scenario analysis.[13] Additionally, as there is uncertainty regarding the additive disutility of pregnancy outcomes on top of the disutility of a UIP, the impact of disutilities associated with pregnancy outcomes was explored in a scenario analysis by setting the disutility for all pregnancy outcomes to zero.

- **A more appropriate approach to estimating costs relating to copper IUDs could have been used.** Copper IUDs available in Canada are indicated for three, five, or 10 years of use. The sponsor assumed that all individuals using a copper IUD would use a three-year copper IUD. In doing so, all individuals on copper IUDs who had not discontinued use over the model time horizon were forced to discontinue use at the end of three years and incurred a cost associated with IUD removal. The clinical expert consulted for this review felt that the majority of individuals using copper IUDs will use a five-year IUD.
    - In the CADTH reanalyses, the cost associated with copper IUD was changed to the average cost of the five-year IUDs identified by CADTH, with prices sourced from the BC PharmaCare Formulary.[28] Additionally, individuals using copper IUDs were not forced to discontinue at the end of the three-year model time horizon.
- **The approach to estimating abortion costs was inappropriate.** To estimate the cost of abortion in the model, the sponsor used codes from the Canadian Institute for Health Information (CIHI) Patient Cost Estimator, using the codes for the following procedure: Abortion diagnosis treated medically, abortion diagnosis with abortive or non-major obstetric and/or gynecologic intervention, abortion diagnosis with fetal anomaly treated medically, and abortion diagnosis with abortive or non-major obstetric and/or gynecologic intervention and fetal anomaly.[29] This approach to costing abortion is limited because the CIHI Patient Cost Estimator reports the average cost of services provided in acute care hospitals.[29] Therefore, using the CIHI Patient Cost Estimator to estimate abortion costs is inappropriate because it does not reflect the outpatient nature of the abortion procedure. Further, the average acute length of stay for all procedure codes used by the sponsor were greater than one day, which is inappropriate because, according to the clinical expert consulted for this review, the majority of patients undergoing an abortion will not be hospitalized.
    - In the CADTH reanalyses, a study by Limacher et al. was used to estimate the cost of medical and surgical abortions in Canada.[30] The reanalyses conservatively assumed that all surgical abortions would occur in hospital.[30] Medical abortion costs were estimated using mifepristone-misoprostol abortion costs from the Limacher et al. study. The costs of both procedures were weighted by the proportion of abortions in Canada in 2017 that were surgical (94%),[31] and this cost was inflated to 2019 values using the Bank of Canada Inflation Calculator.[32]
- **Uncertainty was inappropriately characterized.** Although the analysis was conducted probabilistically, an arbitrary coefficient of variation of 20% of the mean was used to characterize parameter uncertainty for most parameters. This included treatment acquisition costs and costs that are fixed, such as costs sourced from a provincial schedule of benefits should not be included probabilistically. Use of arbitrary variation means that the probabilistic results may not fully reflect the true uncertainty around model parameters. The arbitrary assumption in defining probability distributions is inappropriate as parameters with low sensitivity but higher uncertainty should affect the model's output more than more sensitive parameters that are estimated more precisely.[26]
    - In the CADTH reanalyses, contraceptive costs and costs from provincial schedules of benefits were removed from varying probabilistically.

Key assumptions made by the sponsor and appraised by CADTH are presented in Table 4.

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations in the Submission)

Sponsor's key assumption	CADTH comment
Non-hormonal reversible contraceptive methods not included as data are not readily available.	Uncertain. Data on these methods are available in the review article used by the sponsor to populate efficacy data for the model.[3] However, the costs associated with non-hormonal methods such as condoms would be difficult to estimate.
The proportion of women sexually active and using contraception is constant between age groups.	Unlikely but would be difficult to make assumptions otherwise.
All events occur at the beginning of each year.	Inappropriate. The sponsor utilized a 28-day cycle length but discounted costs and outcomes annually. It is implausible that all events would occur at a single time point in a year.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH reanalyses addressed several limitations within the economic model, as summarized in Table 5. CADTH was unable to address limitations regarding uncertain comparative clinical efficacy, discontinuation rates, and assumptions regarding contraceptive switching. Therefore, although the CADTH reanalysis provides a more accurate picture, it should not be considered a best estimate and should rather be considered alongside the scenario analyses explored in Table 17.

Full results of CADTH's stepped analysis are presented in Table 15. CADTH's reanalysis results demonstrate that, compared with the copper IUD, etonogestrel is $7 more expensive and yields the same average QALY losses, resulting in an ICER of $1,251 (Table 6). In the reanalysis, as with the sponsor's base case, all other options were dominated.

Scenario Analysis Results

As significant uncertainty remained regarding the parameterization of the model and certain assumptions made, CADTH conducted extensive sensitive analyses. Full results are presented in Table 17. As there was no comparative evidence regarding contraceptive efficacy and discontinuation, it is difficult to know the effectiveness and discontinuation of etonogestrel compared to IUS. In a scenario in which the failure rate and discontinuation for etonogestrel were set to be equal to IUS, the ICER of etonogestrel compared to copper IUD increased to $22,528 (all other options remained dominated). Additionally, the role that market shares played on model results was significant. When efficacy and discontinuation for etonogestrel was assumed to be equal to IUS, and all market shares were assumed to be equal, IUS dominated etonogestrel by having lower costs though the same numbers of QALYs.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Changes to derive the CADTH base case		
1. Dropouts	Contraceptive-specific rate of dropout (10% of discontinuations dropout). Dropouts may become pregnant according to age-specific fertility rates, and incur disutility of UIP	100% of discontinuations switch to another contraceptive method 0.22 individuals drop out across contraceptive methods each cycle. Dropouts do not contribute to pregnancy outcomes
2. Disutility of UIP	0.32	0.2006 (= 0.32 × 0.627[a])
3. Price of copper IUD and duration of use	$63.00 over 3 years	$165.39 over 5 years
4. Abortion cost	$2,532	$1,020[b]
5. Uncertainty in costs	Contraceptive and provincial schedule of benefits costs included in probabilistic analysis	Contraceptive and provincial schedule of benefits costs excluded from probabilistic analysis
CADTH base case		1 + 2 + 3 + 4 + 5

IUD = intrauterine device; UIP = unintended pregnancy.

[a] The sponsor's disutility for a UIP was multiplied by the average time spent pregnant in the model. This was calculated by calculating a weighed average of pregnancy outcomes across age groups and summing the overall percentage of pregnancies with each outcome; summing the outcomes of birth, Caesarean sections, and vaginal delivery births to estimate the percentage of outcomes that are full-term births (70.49%) and summing the other pregnancy outcomes (abortion, ectopic pregnancy, and miscarriage) to estimate the percentage of pregnancies that are not full term; and multiplying these percentages by the proportion of the year spent pregnant (nine of 12 months for full-term births and four of 12 months for other birth outcomes). Summing these values equals 0.627.

[b] Cost of abortion estimated as the health care system cost of a medical abortion ($361.93) and a surgical in-hospital abortion ($842.63) weighed by the percentage of abortions that are medical versus surgical (6% versus 94%, respectively), giving a total weighted cost of $814.[30] Inflated from the 2006 to 2020 values using the Bank of Canada Inflation Calculator.[32]

Table 6: Summary of the CADTH Reanalysis Results

Drug	Total costs	Total QALYs	ICER vs. reference	Sequential ICER
CADTH base case				
Copper IUD	760	–0.01	–	–
Etonogestrel	767	–0.01	$7,392	$1,251
IUS	930	–0.01	$169,899	Dominated
Oral contraceptive	1,719	–0.05	$958,755	Dominated
Vaginal ring	1,853	–0.05	$1,092,804	Dominated
Contraceptive patch	1,945	–0.05	$1,184,886	Dominated
Injectable progestin	2,481	–0.04	$1,720,617	Dominated

ICER = incremental cost-effectiveness ratio; IUD = intrauterine device; IUS = intrauterine system; QALY = quality-adjusted life-years; vs. = versus.

Note: Reanalyses are based on publicly available prices of comparators.

Issues for Consideration

Over time, etonogestrel may become less effective in individuals who are overweight. Therefore, health care providers may consider earlier replacement of the implant in heavier women, according to the etonogestrel product monograph.[1] Earlier removal of the implant will decrease the cost-effectiveness of etonogestrel. Additionally, according to the product monograph, all health care professional who administer etonogestrel should receive instruction and training prior to performing insertion and/or removal of the implant.[1] The cost of such training is not included in the analysis.

Overall Conclusions

The CADTH reanalysis showed that etonogestrel is expected to cost $7 more but yield 0.006 fewer QALY losses than the copper IUD, leading to an ICER of $1,251 per QALY. It was shown to be at least as effective and less costly than all other contraceptive options considered. The model lacked robust evidence for key aspects, which limited CADTH's ability to derive a reliable base-case estimate. Instead, key parameters, such as efficacy, are based on assumptions in the CADTH reanalyses.

The annual cost of using etonogestrel is less expensive than most forms of contraception, except for copper IUDs and IUSs, if used for the full three years. The lack of comparative evidence is the main limiting factor as the efficacy and AE profiles of the different contraceptive methods have not been addressed in any way using direct or indirect methods. Although etonogestrel appears economically attractive, this result is grounded in assumptions of comparative effectiveness with other contraceptive methods, mainly IUSs. If it is believed that etonogestrel is as effective and safe as other contraceptive alternatives, then it represents a cost-effective use of health care resources.

Appendix 1: Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing product listing agreements are not reflected in the table; therefore, the table may not represent the actual costs to public drug plans.

Table 7: CADTH Cost Comparisons for Hormonal Contraceptives Indicated for the Prevention of Pregnancy

Treatment	Strength	Form	Price ($)	Recommended dosage	Average daily cost ($)	Average annual cost ($)
Etonogestrel (Nexplanon)	68 mg	Subdermal implant	285.0000[a]	1 implant every 3 years	0.26	95
Intrauterine systems						
Levonorgestrel (Kyleena)	19.5 mg	Intrauterine system	326.0600	1 system every 5 years	0.18	65
Levonorgestrel (Mirena)	52 mg	Intrauterine system	348.4500	1 system every 5 years	0.19	70
Injectable progestin						
Medroxyprogesterone acetate (Depo-Provera)	50 mg/mL 150 mg/mL	Sterile suspension	35.1613 30.4800	150 mg every 3 months	0.39 0.33	141 122
Vaginal ring						
Etonogestrel-ethinyl estradiol	11.4 mg etonogestrel 2.6 mg ethinyl estradiol	Slow release vaginal ring	16.2300[b]	1 ring monthly	0.50	182
Transdermal patch						
Norelgestromin-ethinyl estradiol	6 mg norelgestromin 60 mcg ethinyl estradiol	Transdermal patch	6.8133[c,d]	1 patch weekly (3 patches every 28 days)	0.73	266

Note: All prices are from the Ontario Drug Benefit Formulary (accessed July 2020), unless otherwise indicated, and do not include dispensing fees.[33]

[a] Sponsor-submitted price.

[b] Saskatchewan online formulary (accessed July 2020).[34]

[c] DeltaPA (accessed July 2020).[17]

[d] Price per patch (three patches required per 28 days).

Table 8: CADTH Cost Comparisons for Non-Hormonal, Long-Acting Reversible Therapies Used for the Prevention of Pregnancy

Treatment	Strength	Form	Price ($)	Recommended dosage	Average daily cost ($)	Average annual cost ($)
Flexi-T 300[35]	Copper 300 mm^2	Intrauterine device	226.8000[a]	1 device every 5 years[35]	0.12	45
Flexi-T 300+[35]	Copper 300 mm^2	Intrauterine device	226.8000[a]	1 device every 5 years[35]	0.12	45
Flexi-T 380+[35]	Copper 380 mm^2	Intrauterine device	226.8000[a]	1 device every 5 years[35]	0.12	45
Liberte UT 380 Standard	Copper 380 mm^2	Intrauterine device	110.1600[a]	1 device every 5 years[36]	0.06	22

Treatment	Strength	Form	Price ($)	Recommended dosage	Average daily cost ($)	Average annual cost ($)
Liberte UT 380 Short	Copper 380 mm^2	Intrauterine device	110.1600[a]	1 device every 5 years[36]	0.06	22
Liberte TT 380 Standard	Copper 380 mm^2	Intrauterine device	127.4400[a]	1 device every 10 years[36]	0.03	13
Liberte TT 380 Short	Copper 380 mm^2	Intrauterine device	127.4400[a]	1 device every 5 years[36]	0.07	25
Mona Lisa N[37]	Copper 300 mm^2	Intrauterine device	129.6000[b]	1 device every 3 years[37]	0.12	43
Mona Lisa 5 Standard[37]	Copper 380 mm^2	Intrauterine device	129.6000[b]	1 device every 5 years[37]	0.07	26
Mona Lisa 5 Mini[37]	Copper 380 mm^2	Intrauterine device	63.0000[b]	1 device every 5 years[37]	0.03	13
Mona Lisa 10[37]	Copper 380 mm^2	Intrauterine device	152.8200[a]	1 device every 10 years[37]	0.04	15

[a] BC PharmaCare Formulary Search (accessed July 2020).[28]

[b] DeltaPA (accessed July 2020).[17]

Table 9: CADTH Cost Comparisons for Oral Contraceptives

Treatment	Strength	Form	Price ($)	Recommended dosage	Average daily cost ($)	Average annual cost ($)
Combined oral contraceptives: First-generation progestins						
Norethindrone acetate/ethinyl estradiol (Lolo)	1 mg norethindrone acetate/ 10 mcg ethinyl estradiol	28-tablet pack	17.7688[a]	1 pack every 28 days	0.63	232
Norethindrone acetate/ethinyl estradiol (Minestrin 1/20)	1 mg norethindrone acetate/ 20 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	16.9915 16.9915	1 pack every 28 days	0.61	221
Norethindrone acetate/ethinyl estradiol (Loestrin 1.5/30)	1.5 mg norethindrone acetate/ 30 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	16.9915 16.9915	1 pack every 28 days	0.61	221
Norethindrone/ethinyl estradiol (Brevicon 0.5/35)	0.5 mg norethindrone/ 35 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	14.8200 14.8200	1 pack every 28 days	0.53	193
Norethindrone/ethinyl estradiol (Brevicon 1/35)	1 mg norethindrone/ 35 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	14.8200 14.8200	1 pack every 28 days	0.53	193
Norethindrone/ethinyl estradiol (Synphasic)	1 mg norethindrone/ 35 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	13.4800 13.4800	1 pack every 28 days	0.48	176
Norethindrone/ethinyl estradiol (Select 1/35)	1 mg norethindrone/ 35 mcg ethinyl estradiol	21-tablet pack	10.5900[b] 10.5900[b]	1 pack every 28 days	0.38	138

Treatment	Strength	Form	Price ($)	Recommended dosage	Average daily cost ($)	Average annual cost ($)
		28-tablet pack				
Ethynodiol diacetate/ethinyl estradiol (Demulen)	2 mg ethynodiol diacetate/ 30 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	16.1733 17.3093	1 pack every 28 days	0.58 0.62	211 226
Combined oral contraceptives: Second-generation progestins						
Levonorgestrel/ethinyl estradiol (Alesse, Alysena, Aviane)	100 mcg levonorgestrel/ 20 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	9.7400 9.7400	1 pack every 28 days	0.35	127
Levonorgestrel/ethinyl estradiol (Triquilar)	50/75/125 mg levonorgestrel/ 30/40/30 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	15.75 15.75	1 pack every 28 days	0.56	205
Levonorgestrel/ethinyl estradiol (Min-Ovral, Portia, Ovima)	150 mcg levonorgestrel/ 30 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	7.2800 7.2800	1 pack every 28 days	0.26	95
Levonorgestrel/ethinyl estradiol (Seasonale)	150 mcg levonorgestrel/ 30 mcg ethinyl estradiol	91-tablet pack	59.8780[a]	1 pack every 91 days	0.66	240
Levonorgestrel/ethinyl estradiol (Indayo)	150 mcg levonorgestrel/ 30 mcg ethinyl estradiol	91-tablet pack	45.9641[a]	1 pack every 91 days	0.51	184
Levonorgestrel/ethinyl estradiol (Seasonique)	150 mcg levonorgestrel/ 30 mcg ethinyl estradiol + 10 mcg ethinyl estradiol	91-tablet pack	58.4766[a]	1 pack every 91 days	0.64	235
Combined oral contraceptives: Third-generation progestins						
Desogestrel/ethinyl estradiol (Marvelon, Apri, Freya, Mirvala, Reclipsen)	150 mcg desogestrel/ 30 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	7.7700[c] 7.7700[c]	1 pack every 28 days	0.28	101
Desogestrel/ethinyl estradiol (Linessa)	100/125/150 mcg desogestrel/ 25 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	15.6000 15.6000	1 pack every 28 days	0.56	203
Norgestimate/ethinyl estradiol (Cyclen)	250 mcg norgestimate/ 35 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	28.7500 28.7500	1 pack every 28 days	1.03	375
Norgestimate/ethinyl estradiol (Tri-Cyclen)	180/215/250 mcg norgestimate/ 35 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	28.7500 28.7500	1 pack every 28 days	1.03	375

Treatment	Strength	Form	Price ($)	Recommended dosage	Average daily cost ($)	Average annual cost ($)
Norgestimate/ethinyl estradiol (Tri-Cyclen Lo, Tricera Lo)	180/215/250 mcg norgestimate/ 25 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	9.4725 9.4725	1 pack every 28 days	0.34	123
Combined oral contraceptives: Products containing drospirenone						
Drospirenone/ethinyl estradiol (Yasmin, Qismette)	3 mg drospirenone/ 30 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	12.4400 12.4400	1 pack every 28 days	0.44	162
Drospirenone/ethinyl estradiol (Yaz)	3 mg drospirenone/ 20 mcg ethinyl estradiol	28-tablet pack	16.5200	1 pack every 28 days	0.59	215
Drospirenone/ethinyl estradiol (Yaz Plus)	3 mg drospirenone/ 20 mcg ethinyl estradiol/ 45 mcg levomefolate	28-tablet pack	11.8412[a]	1 pack every 28 days	0.42	154
Progestin-only oral contraceptive						
Norethindrone (Micronor, Jencycla, Movisse)	35 mcg norethindrone	28-tablet pack	10.9900	1 pack every 28 days	0.39	143
Off-label drug therapies used for the prevention of pregnancy						
Cyproterone acetate/ ethinyl estradiol (Diane-35, Cyestra-35, Cleo-35, Ran-Cyproterone, Teva-Cyproterone)	2 mg cyproterone acetate/ 35 mcg ethinyl estradiol	21-tablet pack 28-tablet pack	23.3394	1 pack every 28 days	0.83	304
Cyproterone acetate/ethinyl estradiol (Cleo–35)	2 mg cyproterone acetate/ 35 mcg ethinyl estradiol	21-tablet pack	26.9997[a]	1 pack every 28 days	0.96	352

All prices are from the Ontario Drug Benefit Formulary (accessed July 2020) unless otherwise indicated and do not include dispensing fees.[33,38]

[a] DeltaPA (accessed July 2020).[17]

[b] Saskatchewan online formulary (accessed July 2020).[34]

[c] All prices are from the Ontario Drug Benefit Formulary, apart from Reclipsen, which is from the Saskatchewan formulary (accessed July 2020).

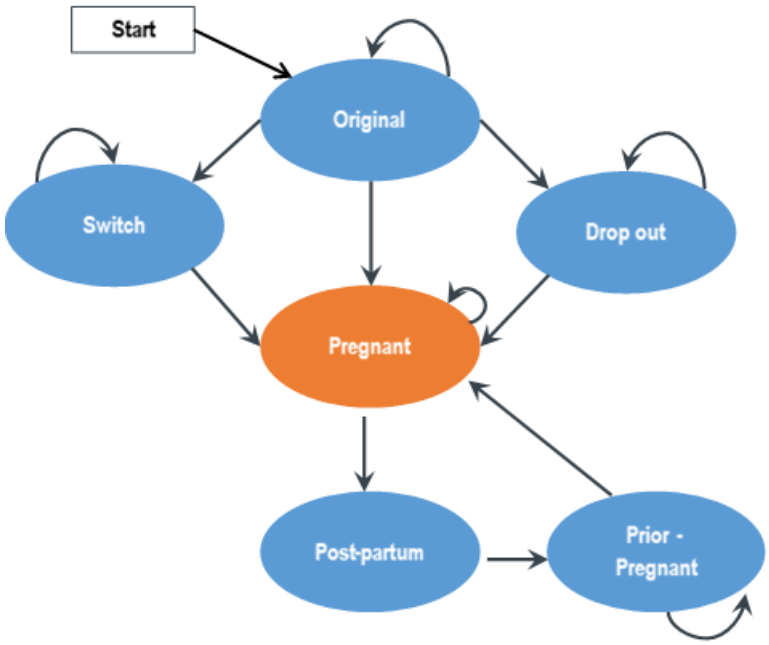
Appendix 2: Submission Quality

Table 10: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☒	☐	
Model has been adequately programmed and has sufficient face validity	☒	☐	
Model structure is adequate for decision problem	☒	☐	
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☐	☒	See “Limitations of Sponsor’s Submission.” Most parameters had an arbitrary coefficient of variation of 20% of the mean to characterize parameter uncertainty.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☒	☐	
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	☒	☐	

Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Model Structure



Source: Sponsor's pharmacoeconomic submission.[2]

Detailed Results of the Sponsor's Base Case

Table 11: Disaggregated Summary of the Sponsor's Economic Evaluation Results

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)	Percentage of total incremental (sequential)
Number of UIPs					
Copper IUD	Original	18			
	Switchers	23			
	Dropouts	3			
	Prior pregnant	1			
	Total	**45**			
Etonogestrel	Original	1	–17	–17	–81.0%
	Switchers	20	–3	–3	–14.3%
	Dropouts	3	0	0	0.0%
	Prior pregnant	0	–1	–1	–4.8%
	Total	**24**	**–21**	**–21**	**–100%**
IUS	Original	4	–14	3	13.0%
	Switchers	39	16	19	82.6%

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)	Percentage of total incremental (sequential)
	Dropouts	3	0	0	0%
	Prior pregnant	1	0	1	4.3%
	Total	**47**	**2**	**23**	**100%**
Injectable progestin	Original	91	73	87	94.6%
	Switchers	38	15	–1	–1.1%
	Dropouts	6	3	3	3.3%
	Prior pregnant	4	3	3	3.3%
	Total	**139**	**94**	**92**	**100%**
OCP	Original	154	136	63	185.3%
	Switchers	8	–15	–30	–88.2%
	Dropouts	5	2	–1	–2.9%
	Prior pregnant	6	5	2	5.9%
	Total	**173**	**128**	**34**	**100%**
Vaginal ring	Original	157	139	3	12.5%
	Switchers	29	6	21	87.5%
	Dropouts	4	1	–1	–4.2%
	Prior pregnant	7	6	1	4.2%
	Total	**197**	**152**	**24**	**100%**
Contraceptive patch	Original	163	145	6	120%
	Switchers	28	5	–1	–20%
	Dropouts	4	1	0	0%
	Prior pregnant	7	6	0	0%
	Total	**202**	**157**	**5**	**100%**
Discounted QALYs losses (by source of QALY loss)					
Copper IUD	Pregnancy	–0.015			
	Pregnancy outcomes	–0.003			
	AEs	0			
	Total	–0.019			
Etonogestrel	Pregnancy	–0.08	0.007	0.007	78%
	Pregnancy outcomes	–0.002	0.002	0.002	22%
	AEs	0	0	0	0%
	Total	**–0.010**	**0.009**	**0.009**	**100%**
IUS	Pregnancy	–0.016	–0.001	–0.008	80%
	Pregnancy outcomes	–0.003	0	–0.002	20%
	AEs	0	0	0	0%
	Total	**–0.019**	**–0.001**	**–0.010**	**100%**
Injectable progestin	Pregnancy	–0.047	–0.032	–0.031	82%
	Pregnancy outcomes	–0.010	–0.007	–0.007	18%
	AEs	0	0	0	0%
	Total	**–0.057**	**–0.039**	**–0.038**	**100%**

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)	Percentage of total incremental (sequential)
OCP	Pregnancy	–0.059	–0.043	–0.011	78%
	Pregnancy outcomes	–0.012	–0.009	–0.002	12%
	AEs	0	0	0	0%
	Total	**–0.071**	**–0.053**	**–0.014**	**100%**
Vaginal ring	Pregnancy	–0.067	–0.051	–0.008	80%
	Pregnancy outcomes	–0.014	–0.011	–0.002	20%
	AEs	0	0	0	0%
	Total	**–0.081**	**–0.062**	**–0.010**	**100%**
Contraceptive patch	Pregnancy	–0.069	–0.053	–0.002	100%
	Pregnancy outcomes	–0.014	–0.011	0	0%
	AEs	0	0	0	0%
	Total	**–0.083**	**–0.065**	**–0.002**	**100%**
Discounted costs ($)					
Copper IUD	Acquisition	196.84			
	Resource utilization	195.15			
	AEs	3.60			
	Pregnancy	295.10			
	Total	**690.69**			
Etonogestrel	Acquisition	369.30	172.49		
	Resource utilization	236.85	41.69		
	AEs	3.07	–0.53		
	Pregnancy	159.11	–135.99		
	Total	**768.36**	**77.67**		
IUS	Acquisition	440.10	243.26	70.77	52%
	Resource utilization	151.86	–43.29	–84.98	–62%
	AEs	6.07	2.47	3	2%
	Pregnancy	306.46	11.37	147.36	108%
	Total	**904.50**	**213.80**	**136.14**	**100%**
Injectable progestin	Acquisition	269.76	72.92	–170.34	–25%
	Resource utilization	393.30	198.14	241.43	36%
	AEs	6.75	3.14	0.67	0%
	Pregnancy	910.57	615.48	604.11	89%
	Total	**11,580.37**	**889.68**	**675.88**	**100%**
OCP	Acquisition	470.37	273.53	200.61	104%
	Resource utilization	145.96	–49.19	–247.33	–128%
	AEs	27.02	23.41	20.27	11%
	Pregnancy	1,129.16	834.06	218.58	114%
	Total	**1,772,502**	**1,081.81**	**192.13**	**100%**
Vaginal ring	Acquisition	572.72	375.88	102.35	46%
	Resource utilization	130.33	–64.82	–15.33	–7%
	AEs	5.87	2.26	–21.15	–10%

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)	Percentage of total incremental (sequential)
	Pregnancy	1,285.03	989.93	155.87	70%
	Total	**1,993.94**	**1,303.25**	**221.44**	**100%**
Contraceptive patch	Acquisition	606.81	409.97	34.09	50%
	Resource utilization	130.07	–65.08	–0.26	–0.4%
	AEs	5.56	1.96	–0.30	–0.4%
	Pregnancy	1,320.06	1,024.97	35.04	51%
	Total	**2,062.51**	**1,371.25**	**68.56**	**100%**
		ICER vs. reference ($)		**Sequential ICER ($)**	
Copper IUD		–		–	
Etonogestrel		9,121		9,121	
IUS		Dominated		Dominated	
Injectable progestin		Dominated		Dominated	
OCP		Dominated		Dominated	
Vaginal ring		Dominated		Dominated	
Contraceptive patch		Dominated		Dominated	

AE = adverse event; ICER = incremental cost-effectiveness ratio; IUD = intrauterine device; IUS = intrauterine system; OCP = oral contraceptive pill; QALY = quality-adjusted life year; UIP = unintended pregnancy.

Table 12: Efficacy Inputs Used by Sponsor

Contraceptive method	Annual failure rate with typical use	Annual discontinuation rates		
		Year 1	Year 2	Year 3
Etonogestrel	0.05%	16%	12%	9%
Intrauterine system	0.20%	20%	15%	11%
Copper intrauterine device	0.80%	22%	17%	12%
Injectable progestin	6.00%	44%	33%	25%
Oral contraceptive pill	9.00%	33%	25%	19%
Contraceptive patch	9.00%	33%	25%	19%
Vaginal ring	9.00%	33%	25%	19%

Source: Sponsor's pharmacoeconomic submission.[2]

Table 13: Contraceptive Market Shares Used by Sponsor

Contraceptive method	Market share
Etonogestrel	10.0%
Intrauterine system	48.1%
Copper intrauterine device	4.5%
Injectable progestin	3.5%
Oral contraceptive pill	31.1%
Contraceptive patch	1.2%
Vaginal ring	1.6%

Source: Sponsor's pharmacoeconomic submission.[2]

Table 14: Disutility Values Used by Sponsor

Disutility	Value	Source
Unintended pregnancy	0.32	Lundsberg et al.[13]
Pregnancy outcomes		
Vaginal delivery	0.08333	Sonnenberg et al.[14]
Caesarean section	0.11540	
Ectopic pregnancy	0.08333	
Abortion	0.03850	
Miscarriage	0.05770	
Adverse events		
Amenorrhea	None due to mildness of condition	Assumption
Venous thromboembolism	0.04	Preblick et al.[16]
Urinary tract infection	0.16	Ellis et al.[15]

Source: Sponsor's pharmacoeconomic submission.[2]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Detailed Results of CADTH Base Case

Table 15: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
Sponsor's base case	Copper IUD	691	–0.02	–
	Etonogestrel	768	–0.01	9,121
	IUS	904	–0.02	Dominated
	Injectable progestin	1,580	–0.06	Dominated
	Oral contraceptive	1,773	–0.07	Dominated
	Contraceptive patch	1,994	–0.08	Dominated
	Vaginal ring	2,063	–0.08	Dominated
CADTH reanalysis 1: Dropouts	Copper IUD	705	–0.02	–
	Etonogestrel	773	–0.01	8,074
	IUS	944	–0.02	Dominated
	Oral contraceptive	1,775	–0.07	Dominated
	Vaginal ring	1,918	–0.07	Dominated
	Contraceptive patch	2009	–0.07	Dominated
	Injectable progestin	2,528	–0.05	Dominated
CADTH reanalysis 2: UIP disutility	Copper IUD	710	–0.01	–
	Etonogestrel	770	–0.01	9,567
	IUS	930	–0.01	Dominated
	Injectable progestin	1,609	–0.04	Dominated
	Oral contraceptive	1,850	–0.05	Dominated
	Vaginal ring	1,985	–0.05	Dominated
	Contraceptive patch	2,073	–0.05	Dominated
CADTH reanalysis 3: Price of 5-year copper IUD	**Etonogestrel**	771	–0.01	–
	Copper IUD	772	–0.02	Dominated
	IUS	930	–0.02	Dominated
	Injectable progestin	1,592	–0.05	Dominated
	Oral contraceptive	1,843	–0.07	Dominated
	Vaginal ring	1,974	–0.08	Dominated
	Contraceptive patch	2,072	–0.08	Dominated
CADTH reanalysis 4: Abortion cost	Copper IUD	688	–0.02	–
	Etonogestrel	762	–0.01	8,359
	IUS	910	–0.02	Dominated
	Injectable progestin	1,544	–0.05	Dominated
	Oral contraceptive	1,775	–0.07	Dominated
	Contraceptive patch	1,897	–0.08	Dominated
	Vaginal ring	1,995	–0.08	Dominated

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
CADTH reanalysis 5: Uncertainty in costs	Copper IUD	705	–0.02	–
	Etonogestrel	770	–0.01	7,253
	IUS	927	–0.02	Dominated
	Injectable progestin	1,593	–0.05	Dominated
	Oral contraceptive	1,841	–0.07	Dominated
	Vaginal ring	1,973	–0.08	Dominated
	Contraceptive patch	2,067	–0.08	Dominated
CADTH base case (1 + 2 + 3 + 4 + 5)	Copper IUD	760	–0.01	–
	Etonogestrel	767	–0.01	1,251
	IUS	930	–0.01	Dominated
	Oral contraceptive	1,719	–0.05	Dominated
	Vaginal ring	1,853	–0.05	Dominated
	Contraceptive patch	1,945	–0.05	Dominated
	Injectable progestin	2,481	–0.04	Dominated

ICER = incremental cost-effectiveness ratio; IUD = intrauterine device; IUS = intrauterine system; QALY = quality-adjusted life-year; UIP = unintended pregnancy.

Table 16: Disaggregated Costs for CADTH's Economic Evaluation Results

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)	Percentage of total incremental (sequential)
Discounted costs					
Copper IUD	Acquisition	310.09			
	Resource utilization	180.12			
	AEs	3.78			
	Pregnancy	266.08			
	Total	**760.07**			
Etonogestrel	Acquisition	391.67	81.58		
	Resource utilization	238.76	58.64		
	AEs	2.96	–0.83		
	Pregnancy	134.07	–132.00		
	Total	**767.46**	**7.39**		
IUS	Acquisition	468.26	158.17	76.59	47%
	Resource utilization	165.77	–14.35	–72.99	–45%
	AEs	6.29	2.50	3.33	2%
	Pregnancy	289.65	23.58	155.58	96%
	Total	**929.97**	**169.90**	**162.51**	**100%**
OCP	Acquisition	509.75	199.66	41.49	5%
	Resource utilization	159.93	–20.19	–5.84	–1%
	AEs	25.48	21.70	19.19	2%
	Pregnancy	1,023.66	757.58	734.01	93%
	Total	**1,718.82**	**958.76**	**788.86**	**100%**
Vaginal ring	Acquisition	535.36	225.27	25.61	19%

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)	Percentage of total incremental (sequential)
	Resource utilization	142.01	–38.11	–17.92	–13%
	AEs	6.11	2.33	–19.37	–14%
	Pregnancy	1,169.40	903.32	145.73	109%
	Total	**1,852.87**	**1,092.80**	**134.05**	**100%**
Contraceptive patch	Acquisition	625.76	315.67	90.40	98%
	Resource utilization	141.81	–38.31	–0.20	0%
	AEs	6.13	2.35	0.02	0%
	Pregnancy	1,171.26	905.18	1.86	2%
	Total	**1,944.96**	**1,184.89**	**92.08**	**100%**
Injectable progestin	Acquisition	611.43	301.34	–14.33	–3%
	Resource utilization	1,045.03	864.91	903.22	169%
	AEs	6.96	3.18	0.83	0%
	Pregnancy	817.27	551.19	–353.99	–66%
	Total	**2,480.69**	**1,720.62**	**535.73**	**100%**

	ICER vs. reference ($)	Sequential ICER ($)
Copper IUD	–	–
Etonogestrel	$1,251	$1,251
IUS	Dominated	Dominated
OCP	Dominated	Dominated
Vaginal ring	Dominated	Dominated
Contraceptive patch	Dominated	Dominated
Injectable progestin	Dominated	Dominated

AE = adverse event; ICER = incremental cost-effectiveness ratio; IUD = intrauterine device; IUS = intrauterine system; OCP = oral contraceptive pill; QALY = quality-adjusted life year; UIP = unintended pregnancy; vs. = versus.

Scenario Analyses

Table 17: CADTH Common Drug Review Scenario Analyses

	Analysis	Comparator	Cost ($)	Total QALY losses	ICER($ per QALY)
	CADTH reanalysis	Copper IUD	760	–0.01	–
		Etonogestrel	767	–0.01	1,251
		IUS	930	–0.01	Dominated
		Oral contraceptive	1,719	–0.05	Dominated
		Vaginal ring	1,853	–0.05	Dominated
		Contraceptive patch	1,945	–0.05	Dominated
		Injectable progestin	2,481	–0.04	Dominated
Efficacy and discontinuation scenarios					
1a	Etonogestrel efficacy equal to IUS efficacy (0.2% failure rate)	Copper IUD	760	–0.01	**Reference**
		Etonogestrel	790	–0.01	6,005
		IUS	930	–0.01	Dominated
		Oral contraceptive	1,716	–0.05	Dominated
		Vaginal ring	1,851	–0.05	Dominated

	Analysis	Comparator	Cost ($)	Total QALY losses	ICER($ per QALY)
		Contraceptive patch	1,942	–0.05	Dominated
		Injectable progestin	2,480	–0.04	Dominated
1b	Etonogestrel discontinuation equal to IUS discontinuation (20%, 15%, and 11% in years 1, 2, and 3, respectively)	Copper IUD	760	–0.01	**Reference**
		Etonogestrel	823	–0.01	13,603
		IUS	929	–0.01	Dominated
		Oral contraceptive	1,718	–0.05	Dominated
		Vaginal ring	1,852	–0.05	Dominated
		Contraceptive patch	**1,944**	**–0.05**	Dominated
		Injectable progestin	**2,480**	**–0.04**	Dominated
1c = 1a + 1b	Etonogestrel efficacy and discontinuation equal to IUS	Copper IUD	761	–0.01	**Reference**
		Etonogestrel	845	–0.01	22,528
		IUS	932	–0.01	Dominated
		Oral contraceptive	1,721	–0.05	Dominated
		Vaginal ring	1,855	–0.05	Dominated
		Contraceptive patch	1,946	**–0.05**	Dominated
		Injectable progestin	2,481	–0.04	Dominated
Market share scenarios					
2a	All products given equal market share (14.29%)	Etonogestrel	827	–0.01	**Reference**
		Copper IUD	866	–0.02	Dominated
		IUS	914	–0.01	Dominated
		Vaginal ring	1,936	–0.06	Dominated
		Oral contraceptive	1,944	–0.06	Dominated
		Contraceptive patch	2,019	–0.06	Dominated
		Injectable progestin	2,633	–0.04	Dominated
2a + 1c	Etonogestrel efficacy and discontinuation equal to IUS, equal market share for all products	Copper IUD	865	–0.02	**Reference**
		IUS	915	–0.01	11,388
		Etonogestrel	920	–0.01	Dominated
		Vaginal ring	1,933	–0.06	Dominated
		Oral contraceptive	1,940	–0.06	Dominated
		Contraceptive patch	2,015	–0.06	Dominated
		Injectable progestin	2,631	–0.04	Dominated
Discontinuation after year 1					
3	Discontinuation 0% in year 2 and 3 for all comparators (no discontinuation after year 1)	Copper IUD	640	–0.01	**Reference**
		Etonogestrel	675	–0.004	5,691
		IUS	789	–0.01	Dominated
		Oral contraceptive	1,809	–0.05	Dominated
		Vaginal ring	1,917	–0.06	Dominated
		Contraceptive patch	2,022	–0.06	Dominated
		Injectable progestin	2,810	–0.04	Dominated
Disutility					
4a	Disutility for UIP: TTO from	Copper IUD	760	–0.003	**Reference**
		Etonogestrel	767	–0.002	4,390

	Analysis	Comparator	Cost ($)	Total QALY losses	ICER($ per QALY)
	Lundsberg[13] ([1 – 0.9996] × 0.627 = 0.0003)	IUS	929	–0.004	Dominated
		Oral contraceptive	1,717	–0.013	Dominated
		Vaginal ring	1,851	–0.015	Dominated
		Contraceptive patch	1,943	–0.015	Dominated
		Injectable progestin	2,477	–0.010	Dominated
4b	Disutility for pregnancy outcomes set to 0	Copper IUD	760	–0.01	**Reference**
		Etonogestrel	767	–0.004	1,660
		IUS	929	–0.01	Dominated
		Oral contraceptive	1,717	–0.03	Dominated
		Vaginal ring	1,851	–0.04	Dominated
		Contraceptive patch	1,943	–0.04	Dominated
		Injectable progestin	2,479	*–0.03*	Dominated
Adverse events					
5	Frequencies of VTE for etonogestrel set equal to oral contraceptives (0.01%)	Copper IUD	759	–0.01	**Reference**
		Etonogestrel	767	–0.01	1,361
		IUS	930	–0.01	Dominated
		Oral contraceptive	1,718	–0.05	Dominated
		Vaginal ring	1,851	–0.05	Dominated
		Contraceptive patch	1,943	–0.05	Dominated
		Injectable progestin	2,480	–0.04	Dominated

ICER = incremental cost-effectiveness ratio; IUD = intrauterine device; IUS = intrauterine system; QALY = quality-adjusted life-year; TTO = time trade-off.

Appendix 5: Submitted BIA and CADTH Appraisal

Key Take-Aways of the BIA

- CADTH identified the following key limitations with the sponsor's analysis:
  - Use of a claims-based approach to estimate the population size introduces uncertainty because it estimates users based on assumptions regarding the number of claims an individual makes annually. Second, it assumes that all individuals use the medication in question for contraception, and would therefore be eligible for etonogestrel, when some users may use these medications for other indications.
  - The number of dispensing fees (13) applied annually for users of oral contraceptive pills, the vaginal ring, and the contraceptive patch is uncertain.
  - Use of a three-year time horizon and applying all acquisition costs at the time of initiation for long-acting reversible contraceptives means that, despite IUSs having a lower annual cost than etonogestrel, etonogestrel is likely to be cost-saving over a three-year time horizon.
  - Removing patient co-payments from a public payer perspective.
- CADTH only conducted scenario analyses on the sponsor's base case given that uncertainties associated with a claims-based approach could not be addressed.
- In a CADTH scenario analysis that applied four dispensing fees annually to users of oral contraceptive pills, the vaginal ring, and the contraceptive patch, it was found that, over three years, etonogestrel is no longer cost-saving (estimated budget impact of $176,966 over three years). A scenario analysis that removed co-payments from annual drug costs in the budget impact analysis (BIA) in Alberta demonstrated that this assumption had little influence on the results.
- Etonogestrel has lower upfront costs than IUS; however, an IUS has a lower annual cost, if both etonogestrel and IUS are taken for a full three and five years, respectively. Therefore, if dispensing fees are not considered, it is likely that etonogestrel will be cost-saving over three years.

Summary of Sponsor's BIA

In the submitted BIA, the sponsor assessed the expected budgetary impact resulting from reimbursing etonogestrel for the prevention of pregnancy from a pan-Canadian public drug program perspective over a three-year time horizon (2021 to 2023).[2] The analysis considered all short- and long-term female-based reversible hormonal contraceptive comparators available in Canada, and included injectable progestin, oral contraception, contraceptive patches, vaginal rings, and IUSs.[2] The sponsor estimated market size using a claims-based approach, using historical provincial public drug plan claims data from IQVIA PharmaStat (first quarter 2016 to first quarter 2020). As the included contraceptive units have different durations of use (i.e., a five-year IUS versus one monthly pack of oral contraceptives), the sponsor standardized claims to represent the duration of use for one unit of each comparator (i.e., one claim for IUS and injections corresponds to a duration of three months and five years, respectively; all other comparators correspond to a duration of 28 days). The number of standard claims for each comparator beyond first quarter 2020 was estimated using forecasted market shares applied to the total number of standard claims. Claims were converted to the number of users per year by assuming one claim represented one user for an IUS for the entire time horizon; dividing annual claims for oral contraceptives, contraceptive patch, and vaginal ring by 13; and dividing annual claims for injectable progestin by four. An adherence rate of 100% was assumed for all short-acting contraceptives. Costs of each product were applied to the number of users, including mark-ups and dispensing fees, and co-pays for Alberta.

Under the new drug scenario, it was assumed that introducing etonogestrel would not increase the number of total users of hormonal contraceptives, as it was assumed that all uptake would come from individuals who would otherwise use one of the comparator products. Uptake of etonogestrel was based on market research and consultation with Canadian experts (Table 18).

Table 18: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as years 1 / 2 / 3, if appropriate)
Target population	
Number of patients eligible for drug under review[a]	
Reference scenario	209,434 / 213,721 / 217,507
New drug scenario	209,434 / 210,675 / 207,807
Market uptake (3 years)	
Share of users going to etonogestrel, by type of contraception[b]	
IUS	0.5% / 1.0% / 2.0%
Injectable progestin	6.0% / 9.0% / 15.0%
Oral contraceptives	1.0% / 3.0% / 6.0%
Contraceptive patch	1.0% / 3.0% / 6.0%
Vaginal ring	1.0% / 3.0% / 6.0%
Number of users distributed across treatments (reference scenario)	0 / 0 / 0
Etonogestrel	37,540 / 38,310 / 39,071
IUS	26,544 / 26,310 / 26,110
Injectable progestin	141,434 / 145,184 / 148,405
Oral contraceptives	1,665 / 1,692 / 1,718
Contraceptive patch	2,251 / 2,225 / 2,203
Vaginal ring	
Number of users distributed across treatments (new drug scenario)	3,233 / 7,036 / 12,909
Etonogestrel	37,352 / 37,929 / 38,293
IUS	24,952 / 22,493 / 18,949
Injectable progestin	140,019 / 139,457 / 134,117
Oral contraceptives	1,649 / 1,625 / 1,552
Contraceptive patch	2,229 / 2,137 / 1,988
Vaginal ring	
Cost of treatment (per patient)	
Cost of treatment over one year (including mark-ups, dispensing fees, and co-pays, where applicable)[c]	
Etonogestrel	$293.83[d]
IUS	$334.89 to $357.22[d]
Injectable progestin	$166.99 to $187.21
Oral contraceptives	$114.79 to $518.87
Contraceptive patch	$401.77
Vaginal ring	$338.14

IUS = intrauterine system.

[a] Note there is a difference in the total number of users in years 2 and 3 between the reference and new drug scenarios because the budget impact analysis only captures patients who are making claims. Because the total number of users of long-acting reversible contraceptives (LARC) increases when etonogestrel becomes available (by 3,046 in year 1 and 6,654 in year 2), the number of claims, and, therefore, users, of short-term contraceptives decreases accordingly in the new drug scenario by 3,046 in year 2 and by 3,046 + 6,654 (9,700) in year 3. That is, if a patient initiates a LARC, they are removed from the pool of users in subsequent years.

[b] Note: For each year, the number of etonogestrel users is calculated as the number of users of a comparator in each year multiplied by the expected market share (as presented) that etonogestrel will capture from each comparator. For example, 0.5% of IUS patients in the first year of the reference scenario will receive etonogestrel (i.e., 37,540 × 0.5% = 188 new etonogestrel users from IUS).

[c] Jurisdiction specific drug costs were used. The costs presented are from Ontario.

[d] These contraceptives last more than one year; therefore, the entire cost of the contraceptive is presented.

Summary of the Sponsor's BIA Results

Results of the sponsor's BIA base case indicated an incremental budget impact of $257,283 in year 1, –$284,018 in year 2 and –$1,697,045 in year 3 for a total budget impact over three years of –$1,723,779. Negative values indicate that the sponsor estimates reimbursement of etonogestrel to be cost-saving.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Use of a claims-based approach introduces uncertainty in the estimated budget impact results.** The sponsor's claims-based approach to calculating population size uses the number of claims for currently reimbursed contraceptives to determine the number of patients who would be eligible for etonogestrel. A claims-based approach introduces significant uncertainty into the BIA findings. First, the number of patients derived must be interpreted with caution as it is based on a calculation from claims data. For example, the number of claims of a given oral contraceptive was divided by the number of units required per year for contraception for one individual (13) to estimate the number of users of that comparator. This approach is uncertain because it assumes that all users will continue on a medication for a year, that all users will take all units dispensed, that no doses are missed, and that no packs are taken consecutively (i.e., to avoid a period). Second, some medications might be used by patients for indications other than pregnancy prevention. For example, an IUS is indicated both for the prevention of pregnancy and for the treatment of menorrhagia; however, all IUS users in this claims-based BIA were assumed to be using the IUS for contraception.[39] A more appropriate approach would have been to retrieve claims information for products with multiple indications by indication, and remove claims that were not for the indication of pregnancy prevention. Therefore, the sponsor's claims-based approach includes patients who are using medications for reasons other than contraception as potential eligible users for etonogestrel.
    - Despite being uncertain, CADTH was unable to address the limitations of a claims-based approach in reanalyses.
- **The majority of cost savings for etonogestrel are achieved through dispensing fees.** A scenario analysis on the sponsor's BIA demonstrates that when dispensing fees are removed from the analysis, etonogestrel is no longer cost-saving (three-year total increases to $1,298,168). In the sponsor's analysis, patients taking oral contraceptive pills, the contraceptive patch, or the vaginal ring had 13 dispensing fees applied annually. The assumption that patients are dispensed one unit at a time is highly uncertain. According to a CIHI report, most jurisdictions permit a 90- or 100-day supply for longer-term prescriptions, but this is dependent on prescriber practices and patient monitoring and reassessment needs.
    - As a scenario analysis, CADTH examined the influence of dispensing fees on BIA results by assuming that all short-term contraceptives will be dispensed four times annually in all jurisdictions.
- The realization of benefits associated with the use of long-term reversible contraceptives is inadequately captured in a three-year BIA. In the sponsor's BIA, all acquisition costs for etonogestrel and IUS are incurred in the year of treatment initiation. However, for all IUS patients and for etonogestrel patients who start in years 2 and 3, the full costs offset by initiating a long-acting reversible contraceptive are not captured in a three-year BIA time horizon if patients remain on the medication for its maximum duration of use. Additionally, as the upfront cost of an IUS is higher than that of etonogestrel, using a three-year time horizon means that etonogestrel cannot be cost-saving relative to an

IUS despite IUSs having lower annual costs (if both are used for their maximum duration). If, for example, all current IUS users switched to etonogestrel, this would introduce cost savings in a three-year budget but would add costs in the longer term as patients would need etonogestrel more frequently than had they remained using an IUS. This is not a limitation of the sponsor's approach, but rather a limitation of the structure of a three-year BIA. When considering the budget impact of etonogestrel beyond three years, the cost savings of contraceptive options that are dispensed less frequently should be considered.

- **The appropriateness of removing co-payment costs from a public payer perspective is uncertain.** In the sponsor's BIA, co-payments in Alberta were included in the base-case analysis. There is uncertainty associated with including co-payments in the public payer perspective as jurisdictions may implement different co-payment systems, and because co-payments are typically inclusive of all treatments patients are taking. Therefore, other treatments patients receive that are unrelated to pregnancy prevention may influence the co-payment.
    - As the implementation of co-payments is uncertain and varies across jurisdictions, CADTH explored not considering co-payments for Alberta as a scenario analysis.

Additional limitations were identified but were not considered to be key limitations. These limitations included not including copper IUDs in the analysis despite being listed on the BC PharmaCare Formulary.[28]

CADTH Reanalyses of the BIA

CADTH was unable to address limitations associated with the claims-based approach. A scenario analysis was conducted to address uncertainty regarding the application of dispensing fees. If four dispensing fees were applied per year in all jurisdictions for oral contraceptives, contraceptive patches, and vaginal rings, rather than the sponsor's assumption of 13, introducing etonogestrel would no longer be cost-saving over three years (Table 19). It should be noted that the distribution of contraceptives across patients in this analysis was assumed to be the same as in the sponsor's base case. CADTH also conducted a scenario analysis in which co-payments were not considered in Alberta.

Table 19: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	3-year total
Submitted base case	Reference	$60,226,899	$61,536,582	$62,662,581	$63,643,563	$187,842,726
	New drug	$60,226,899	$61,793,865	$62,378,563	$61,946,518	$186,119,946
	Budget impact	***$0***	***$257,283***	***–$284,018***	***–$1,697,045***	***–$1,723,779***
CADTH scenario analysis: Applying 4 annual dispensing fees for all SARCs	Reference	$47,990,826	$48,948,307	$49,779,783	$50,507,488	$149,235,578
	New drug	$47,990,826	$49,331,473	$50,004,361	$50,076,710	$149,412,544
	Budget impact	***$0***	***$383,166***	***$224,578***	***–$430,778***	***$176,966***
CADTH scenario analysis: Co-payment excluded in Alberta	Reference	$60,498,169	$61,803,811	$62,926,772	$63,905,279	$188,635,862
	New drug	$60,498,169	$62,058,951	$62,634,116	$62,187,130	$186,880,197
	Budget impact	***$0***	***$235,140***	***–$292,656***	***–$1,718,149***	***–$1,755,665***

BIA = budget impact analysis; SARC = short-acting reversible contraceptive.

References

1. Nexplanon (etonogestrel extended release subdermal implant): extended release implant, 68 mg per implant (to deliver up to 70 mcg etonogestrel per day), subdermal [product monograph]. Kirkland (QC): Merck Canada Inc.; 2020 May 25.
2. Pharmacoeconomic evaluation. In: CDR submission: Nexplanon (etonogestrel extended release subdermal implant 68mg radiopaque) [**CONFIDENTIAL** sponsor's submission]. Kenilworth (NJ): Merck & Co, Inc; 2020 May.
3. Trussell J. Contraceptive failure in the United States. *Contraception.* 2011;83(5):397-404.
4. Trussell J. Letter to the editor. *Contraception.* 2008;78(1).
5. Kost K, Singh S, Vaughan B, Trussell J, Bankole A. Estimates of contraceptive failure from the 2002 National Survey of Family Growth. *Contraception.* 2008;77(1):10-21.
6. Sivin I, Stern J. Long-acting, more effective copper T IUDs: a summary of U.S. experience, 1970-75. *Stud Family Planning.* 1979;10(10):263-281.
7. Sivin I, el Mahgoub S, McCarthy T, et al. Long-term contraception with the levonorgestrel 20 mcg/day (LNg 20) and the copper T 380Ag intrauterine devices: a five-year randomized study. *Contraception.* 1990;42(4):361-378.
8. Luukkainen T, Allonen H, Haukkamaa M, et al. Effective contraception with the levonorgestrel-releasing intrauterine device: 12-month report of a European multicenter study. *Contraception.* 1987;36(2):169-179.
9. Cox M, Tripp J, Blacksell S. Clinical performance of the levonorgestrel intrauterine system in routine use by the UK Family Planning and Reproductive Health Research Network: 5-year report. *J Fam Plann Reprod Health Care.* 2002;28(2):73-77.
10. Graesslin O, Korver T. The contraceptive efficacy of Implanon: a review of clinical trials and marketing experience. *Eur J Contracept Reprod Health Care.* 2008;13 Suppl 1:4-12.
11. Provencher C, Milan A, Hallman S, D'Aoust C. Fertility: overview, 2012 to 2016. Ottawa (ON): Statistics Canada; 2018: https://www150.statcan.gc.ca/n1/pub/91-209-x/2018001/article/54956-eng.htm. Accessed 2019 Nov 15.
12. Trussell J, Lalla AM, Doan QV, Reyes E, Pinto L, Gricar J. Cost effectiveness of contraceptives in the United States. *Contraception.* 2009;79(1):5-14.
13. Lundsberg LS, Xu X, Schwarz EB, Gariepy AM. Measuring health utility in varying pregnancy contexts among a diverse cohort of pregnant women. *Contraception.* 2017;96(6):411-419.
14. Sonnenberg FA, Burkman RT, Hagerty CG, Speroff L, Speroff T. Costs and net health effects of contraceptive methods. *Contraception.* 2004;69(6):447-459.
15. Ellis AK, Verma S. Quality of life in women with urinary tract infections: is benign disease a misnomer? *J Am Board Fam Pract.* 2000;13(6):392-397.
16. Preblick R, Kwong WJ, White RH, Goldhaber SZ. Cost-effectiveness of edoxaban for the treatment of venous thromboembolism based on the Hokusai-VTE study. *Hospital Practice.* 2015;43(5):249-257.
17. DeltaPA. [Ottawa (ON)]: IQVIA; 2019: https://www.iqvia.com/. Accessed 2019 Nov 14.
18. Best Start Resource Centre. Routine prenatal care. 2019; https://www.ontarioprenataleducation.ca/routine-prenatal-care/. Accessed 2019 Nov 14.
19. Ontario Case Costing Initiative (OCCI). Toronto (ON): Ontario Health and Long-Term Care; 2018: https://www.ontario.ca/data/ontario-case-costing-initiative-occi. Accessed 2019 Nov 15.
20. Giving birth in Canada: the costs. Ottawa (ON): Canadian Institute for Health Information; 2006: https://secure.cihi.ca/free_products/Costs_Report_06_Eng.pdf. Accessed 2019 Nov 15.
21. Ontario Ministry of Health Long-Term Care. Schedule of benefits for physician services under the Health Insurance Act: effective March 1, 2016. Toronto (ON): The Ministry of Health and Long-Term Care; 2015: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20181115.pdf. Accessed 2019 Nov 15.
22. Clinical Overview: R&D release report ODIN: INT00065117 [**CONFIDENTIAL** internal sponsor's report]. Kirkland (QC): Merck Canada Inc.; 2010 Mar.
23. Clinical Study Report: 34528. A randomized, double-blind, parallel group, bioequivalence study of Implanon® and radiopaque Implanon. [**CONFIDENTIAL** internal sponsor's report]. Kenilworth (NJ): Schering-Plough Research Institute; 2009 Apr.
24. Merck Canada Inc. response to November 28 request for additional information regarding etonogestrel review: Percentage of patients who discontinued their etonogestrel treatment during the study period, broken down by reasons and by specific time periods, for the integrated analysis, P05702 and PN 34528. [**CONFIDENTIAL** additional sponsor's information]. Kirkland (QC): Merck Canada Inc.; 2019 Dec 6.
25. Guertin JR, Feeny D, Tarride J-E. Age- and sex-specific Canadian utility norms, based on the 2013-2014 Canadian Community Health Survey. *CMAJ.* 2018;190(6):E155-E161.
26. Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/dv/guidelines-economic-evaluation-health-technologies-canada-4th-edition. Accessed 2019 Nov 15.
27. Schwarz EB, Smith R, Steinauer J, Reeves MF, Caughey AB. Measuring the effects of unintended pregnancy on women's quality of life. *Contraception.* 2008;78(3):204-210.

28. B. C. Government. BC PharmaCare formulary search. 2019; https://pharmacareformularysearch.gov.bc.ca. Accessed 2020 Jul 23.
29. CIHI. Patient Cost Estimator. https://www.cihi.ca/en/patient-cost-estimator. Accessed 2020 Jul 22.
30. Limacher JJ, Daniel I, Isaacksz S, et al. Early abortion in Ontario: options and costs. *J Obstet Gynaecol Can.* 2006;28(2):142-148.
31. Popinchalk A, Sedgh G. Trends in the method and gestational age of abortion in high-income countries. *BMJ Sex Reprod Health.* 2019.
32. Bank of Canada. Inflation calculator. 2019; https://www.bankofcanada.ca/rates/related/inflation-calculator/. Accessed 2019 Nov 15.
33. Ontario Ministry of Health Long-Term C. Ontario drug benefit formulary/comparative drug index. 2020; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2020 July 23.
34. Government of Saskatchewan. Saskatchewan online formulary database. 2020; http://formulary.drugplan.ehealthsask.ca/SearchFormulary. Accessed 2020 Jul 23.
35. Trimedic Supply Network Ltd. Flexi-T safety and efficacy. 2018; https://www.trimedic-inc.com/flexi-t-safety-and-efficacy/. Accessed 2019 Nov 15.
36. Medisafe Distribution Inc. Liberte IUDs. 2019; http://medisafecanada.com/products/liberte-iuds/. Accessed 2019 Nov 15.
37. Searchlight Pharma. Which MONA LISA® IUD to recommend? 2018; http://www.monalisaiud.ca/hcp/which-mona-lisa-iud-to-recommend/, 2019 Nov 18.
38. Perrault L, Dahan S, Iliza AC, LeLorier J, Zhanel GG. Cost-effectiveness analysis of fosfomycin for treatment of uncomplicated urinary tract infections in Ontario. *Can J Infect Dis Med Microbiol.* 2017;2017:11.
39. Mirena (Levonorgestrel-releasing Intrauterine System, 52 mg [product monograph]. 2019 Jun 14: https://pdf.hres.ca/dpd_pm/00052289.PDF.