Canadian Journal of Health Technologies
April 2024 Volume 4 Issue 4

CADTH Reimbursement Recommendation

Drospirenone (Slynd)

Indication: For conception control in adolescent and adult women
Sponsor: Duchesnay Inc.
Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Slynd?

CADTH recommends that Slynd should be reimbursed by public drug plans for conception control in adolescent and adult women if certain conditions are met.

Which Patients Are Eligible for Coverage?

Slynd should be covered for conception control in adolescent and adult women provided that Slynd is listed in a similar way to other oral contraceptive pills currently reimbursed by public drug plans for the prevention of pregnancy.

What Are the Conditions for Reimbursement?

Slynd should only be reimbursed if the cost does not exceed that of other progestin-only pills (POPs) for contraception.

Why Did CADTH Make This Recommendation?

- Evidence from 3 clinical trials demonstrated that Slynd was effective in preventing pregnancy in adult women.
- Slynd may meet patients' needs for improved convenience with its more flexible administration schedule.
- In the absence of any comparative or indirect evidence, the committee determined that the drug cost of Slynd should not exceed the total drug cost of other POPs.
- Based on the assumption that Slynd would only displace norethindrone, an identically priced comparator, Slynd is expected to have no impact on drug plan budgets over the next 3 years. However, the actual budget impact is uncertain because of the potential for displacement of contraceptives other than POPs.

Additional Information

What Is Conception Control?

Unintended pregnancies are pregnancies that are either unwanted (occurring when no child or no more children are desired) or mistimed (occurring earlier than desired). Most of the unintended pregnancies are a result of not using contraception control or using it inconsistently or incorrectly. It is estimated that nearly 50% of all pregnancies are unintended, and in Canada there were 180,733 unintended pregnancies among women aged 18 to 44 years in 2015.

Summary

Unmet Needs for Patients Seeking Conception Control

Patients need effective hormonal contraceptive pills that are safe, convenient, provide options for women with complex medical conditions, and are accessible.

How Much Does Slynd Cost?

Treatment with Slynd is expected to cost approximately $143 per patient annually.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that drospirenone be reimbursed for conception control in adolescent and adult women only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Three phase III, multicentre clinical trials (Study 301, Study 302, and Study 303) demonstrated that treatment with drospirenone (4 mg tablet daily for 24 days followed by a 4-day hormone-free interval) resulted in contraceptive efficacy in adult women of reproductive age. A pooled analysis based on data from the European Studies, 301 and 302, demonstrated that, based on 8 on-drug pregnancies, drospirenone resulted in an overall Pearl Index (PI) of 0.73 pregnancies per 100 person-years (PY) (95% confidence interval [CI], 0.31 to 1.43; 14,329 exposure cycles) and a corrected PI of 0.79 (95% CI, 0.31 to 1.56; 13,168 cycles with sexual activity and no backup contraception). With a PI of less than 1 and a difference between the PI and the upper limit of the 95% CI of less than 1, drospirenone fulfilled the European Medicines Agency criterion of an effective hormonal contraceptive. Study 303, conducted in the US, demonstrated that based on 12 on-drug pregnancies, drospirenone resulted in an overall PI of 2.4 (95% CI, 1.2 to 4.2; 6,566 exposure cycles) and a PI from evaluable cycles of 2.6 (95% CI, 1.3 to 4.5; 6,004 evaluable cycles); with the upper limit of the 95% CI below 5, drospirenone met the FDA requirements for contraceptive efficacy. Results in subsets of women aged 35 years or younger were supportive of the findings in the overall populations across the 3 studies. CDEC was unable to determine the comparative efficacy of drospirenone compared to other POPs currently available in Canada, since none of the 3 studies performed comparative efficacy analyses.

In the absence of a patient group submission to CADTH for this review, CDEC deliberated on patient needs and preferences identified by the clinical expert consulted by CADTH. Patients have a need for effective hormonal contraceptive pills that may provide improved convenience, have fewer adverse events (AEs), and provide an additional contraceptive option for patients who have contraindications for estrogen-containing contraceptives. CDEC concluded that drospirenone may meet some of the patient needs for improved convenience by allowing a 24-hour missed-pill window without the need for backup contraception; however, no evidence was available assessing the impact of drospirenone's administration schedule on efficacy, safety, or tolerability outcomes. CDEC noted that drospirenone appeared well-tolerated and no new safety concerns were observed, however, the comparative safety of drospirenone versus relevant comparators remains unknown.

The sponsor-submitted price for drospirenone is identical to the publicly listed price for norethindrone. In the absence of any comparative or indirect evidence, the total drug cost of drospirenone should not exceed the total drug cost of norethindrone.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. List in a similar manner to other OCPs for conception control in adolescents and adults.	There was no evidence available to demonstrate how drospirenone compared to other relevant and available OCPs.	—
Pricing		
2. Drospirenone should be negotiated so that it does not exceed the drug program treatment cost of other POPs.	No comparative or indirect evidence was submitted by the sponsor. As such, there is insufficient evidence to justify a cost premium for drospirenone compared to other POPs.	—

POP = progestin-only pill (contraceptive); OCPs = oral contraceptive pills.

Discussion Points

- CDEC deliberated on the contraceptive needs in adolescent and adult women. CDEC discussed that the goals of hormonal contraceptives are to prevent pregnancy, to be safe, accessible, and convenient to use. CDEC noted that POPs are currently available in Canada with an administration schedule that allows a missed-pill window of 3 hours without the need for backup contraception. CDEC heard from the clinical expert that patients value flexible over strict administration schedules for hormonal contraceptives. CDEC agreed with the clinical expert that drospirenone' dosing schedule, which allows a delay of up to 24 hours without the need for backup contraception, may be more convenient to use for patients. The committee noted, however, that once the missed-pill window for drospirenone has closed, backup contraception should be used for 7 days, which may pose a burden to some users. CDEC concluded that there was no evidence assessing the impact of drospirenone's administration schedule on efficacy, safety, tolerability, or health-related quality of life outcomes.
- CDEC discussed the available evidence of drospirenone in adolescent women. Women younger than 18 years old, were excluded from Studies 301 and 302. Study 303 allowed patients aged 15 and older to participate, however, no adolescents enrolled in the trial. CDEC heard from the clinical expert that contraceptive efficacy findings in adult women can be generalized to adolescents as hormonal responses to contraceptive pills are expected to be similar in adolescent and adult women. Drospirenone's safety profile from a phase III, open-label trial (Study 304; N = 102), that assessed the safety and tolerability of drospirenone in adolescents aged 12 to 17 years, appeared consistent with safety results observed in Studies 301, 302, and 303.
- Due to the absence of comparative data for a relevant comparator in Study 301, Study 302, and Study 303, the GRADE assessment concluded that the evidence is very uncertain about the effect of drospirenone on overall PI, corrected PI, PI for evaluable cycles, acceptability, and harms when compared to any comparator. CDEC concluded that despite the low GRADE assessment, results of the trials demonstrated that drospirenone was efficacious as an oral contraceptive. However, CDEC

discussed that the lack of comparative data, especially for AEs, was a major evidence gap associated with drospirenone.

- CDEC recognized that vaginal bleeding patterns are considered important outcomes for patients when selecting a contraceptive method. CDEC heard from the clinical expert that POPs may be associated with unpredictable and irregular bleeding, which may negatively affect a person's acceptance of these contraceptive methods. CDEC noted that across Studies 301, 302, 303, and 304, unscheduled bleeding was common, with 52% to 65% of patients reporting unscheduled bleeding or spotting during the last treatment period. The proportion of patients who discontinued drospirenone due to bleeding-related AEs ranged from 3.3% to 6.0% across the 4 trials. Given the lack of comparative data, and potential bias due to missing data, CDEC was unable to determine how the vaginal bleeding outcomes observed with drospirenone compared to other POPs.
- CDEC noted that none of the available studies included patients with specific comorbidities, such as cardiovascular, renal, or liver disease, diabetes with vascular involvement, psychiatric or substance use disorders, and those with a higher risk of venous thromboembolism (VTE). CDEC concluded that the efficacy and safety of drospirenone in patients who were excluded from the available evidence was unknown. CDEC discussed that while a minority of patients in Study 303 were breastfeeding, they were not included in the trial's efficacy analyses. CDEC heard from the clinical expert that, historically, progestin-only products have been used in women who are breastfeeding and the Health Canada Product Monograph for drospirenone suggests that drospirenone may be preferred over combined oral contraceptives (COCs) in women who are breastfeeding.
- The sponsor submitted a cost-minimization analysis comparing drospirenone to POPs. However, CDEC noted that there are other forms of prescription contraceptives available that are less costly than drospirenone. Additionally, there was no comparative clinical evidence available for drospirenone versus any appropriate comparator; thus, the cost-effectiveness is unknown. Furthermore, the sponsor's budget impact analysis proposed no impact to drug plan budgets with the addition of drospirenone. However, should drospirenone displace lower-cost contraceptive products, which is anticipated to be unlikely based on clinical expert feedback, or should drospirenone's use extend beyond the current POP landscape, increases in budget expenditures may occur.

Background

Unintended pregnancies are pregnancies that are either unwanted (occurring when no child or no more children are desired) or mistimed (occurring earlier than desired). Most of the unintended pregnancies are a result of not using contraception, i.e., birth control, or using it inconsistently or incorrectly. The Society of Obstetricians and Gynecologists of Canada states that nearly 50% of all pregnancies in Canada are unintended. The annual number of unintended pregnancies in Canada was estimated at 180,733 in 2015 among women aged 18 to 44 years, with 58% occurring in women aged between 20 and 29 years. Furthermore, imperfect contraceptive use accounted for 69% and 82% of annual unintended pregnancies in women aged 18 to 44 years and those 20 to 29 years, respectively. Factors associated with unintended

pregnancies among women in Canada were maternal sociodemographic factors such as age, immigration status, level of education, presence of a partner, experience of violence, past pregnancy, smoking, and alcohol or drug use before pregnancy.

Various types of hormonal and nonhormonal contraceptive options are currently recommended in Canada, including both long-acting reversible contraceptives (i.e., intrauterine devices [IUDs] and implants) and short-acting reversible contraceptives (i.e., combined oral contraceptive [COCs], progestin-only pills [POPs], transdermal patches, vaginal rings, injectables). The currently available and reimbursed POPs in Canada all contain 0.35 mg of norethindrone. Norethindrone may be used by most women, including those who have contraindications to estrogen or for which estrogen is less appropriate, such as lactating women. However, norethindrone 0.35 mg daily does not reliably inhibit ovulation, and must be administered at precisely the same time each day. The use of back up contraception is recommended for patients who have missed a dose by more than 3 hours. POPs are also associated with unpredictable and irregular bleeding, which is a common reason for discontinuation. With POPs, interpreting signs and symptoms of pregnancy may be difficult, due to the frequency of unscheduled bleeding and spotting.

Drospirenone has been approved by Health Canada for conception control in adolescent and adult women. Drospirenone is a progestin-only oral contraceptive, which is formulated as 24 tablets of 4 mg drospirenone and 4 inert tablets for oral administration once daily for 28 consecutive days.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 single-arm studies and 1 randomized trial in adult and adolescent women and supplementary evidence from 1 single-arm study in adolescents
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise in conception control in women
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Clinician Input

Input From Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH noted that contraception should be safe, accessible, affordable, reliable, effective, easy to use and reversible (for those who seek that). The availability of diverse options can help satisfy a multitude of patient needs and preferences. Unmet needs include options that are affordable for all, have reduced adverse effects, offer improved convenience, and improved options for those with

complex medical conditions. Oral options allow contraception to be under the patient's control, as the therapy can be started and stopped as desired.

According to the clinical expert, drospirenone may be used by most patients, including those who cannot tolerate estrogen-containing therapies or who are breastfeeding. The expert anticipated that drospirenone will shift the treatment paradigm for those that require an oral progestin-only contraceptive method, and it will have wide and relevant use for noncontraceptive benefits in the management of abnormal uterine bleeding and endometriosis, and for its antiandrogenic effects.

Drospirenone is contraindicated in those with renal impairment, hepatic impairment, and adrenal insufficiency as well as those with general contraindications to hormonal contraception such as pregnancy, or undiagnosed vaginal bleeding. The expert expected drospirenone to have similar treatment effect in adults and adolescents as hormonally these patients are considered the same.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The clinical trials were prospective, multicentre noncomparative studies. The authors suggested that the POP, drospirenone, would have comparable efficacy to COCs which contain a combination of drospirenone and estrogen (e.g., Yaz). The drug plans noted that drospirenone may displace norethindrone as POP. Drospirenone has a 24-hour window for late doses compared to norethindrone which has a three-hour window. • Are the most relevant comparators POPs (i.e., norethindrone)? • Could this drug replace some use of COCs such as combinations of drospirenone and estrogen (e.g., Yaz)?	CDEC agreed with the clinical expert that norethindrone is the most relevant comparator to drospirenone. The clinical expert anticipated that drospirenone would largely replace norethindrone, as, in their opinion, drospirenone was likely more effective. CDEC and the clinical expert did not anticipate that drospirenone would shift the treatment paradigm for COC use, as COCs have some noncontraceptive benefits related to estrogen, and less spotting than POPs.
Considerations for initiation of therapy	
• Could experts anticipate this medication being prescribed independent of its contraceptive effects (e.g., antiandrogenic effects – reduce acne, decrease hirsutism)? • Is there potential for off-label use of drospirenone for noncontraceptive indications?	CDEC agreed with the clinical experts that drospirenone may be used off-label for its antiandrogenic properties and for the management of abnormal uterine bleeding and endometriosis care. However, CDEC noted clinical expert's input that off-label use would likely be limited to a small patient population, given the availability of other off-label options with antiandrogenic properties and the potential for vaginal bleeding and or spotting with drospirenone.
The drug plans note that all other contraceptives are open benefit.	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
Considerations for prescribing of therapy	
The drug plans note that contraceptives may be prescribed by primary care providers, including pharmacists in some jurisdictions. Drospirenone is given once daily for 24 days with 4 days hormone-free tabs.	Comment from the drug programs to inform CDEC deliberations.
Generalizability	
Two of the clinical trials included > 99% of women who were white, and 5% of patients had a BMI > 30 kg/m^2. However, it is estimated (according to Statistics Canada) that approximately 27% of women in Canada have BMI > 30 kg/m^2. A third clinical trial enrolled a population that was more racially diverse, with 35% of patients who had a BMI > 30 kg/m^2. Considering the characteristics of the patients enrolled in the trials, does this limit the external validity of the trial's findings?	CDEC noted the clinical expert's input on the external validity of the key trials. The clinical expert consulted did not raise any substantial concerns regarding the generalizability of the trial populations to the clinical context in Canada, even though the clinical trial population may not fully reflect the diversity of patients seeking contraception in practice.
System and economic issues	
Drug plans suggested same pricing for drospirenone as generic norethindrone ($10.99/box). Drug plans noted that the submitted budget impact assessment suggested drospirenone will have 90% of market share in 3 years. Drug plans stated that they prefer reduced cost as opposed to restrictions to obtain value.	Comment from the drug programs to inform CDEC deliberations.

BMI = body mass index; COC = combination oral contraceptive; POP = progestin-only pill (contraceptive).

Clinical Evidence

Systematic Review

Description of Studies

The systematic review included 3 studies of drospirenone in adult women at risk of pregnancy. The primary objective of the trials were to demonstrate contraceptive efficacy of drospirenone, and the secondary objectives were to demonstrate safety and tolerability. Study 301 and 303 were open-label, noncomparative phase III trials, where all patients received drospirenone for 13 cycles of 28 days. Each cycle consisted of 24 days of drospirenone 4 mg once daily, followed by inert tablets for 4 days. Study 302 was a double-blind, randomized controlled trial (RCT), that randomized patients to drospirenone 4 mg for 9 28-day cycles or desogestrel 0.075 mg daily. The primary and secondary efficacy outcomes of interest to this review were the overall PI, corrected PI, and the PI for evaluable cycles for the drospirenone treatment groups. The PI is the number of pregnancies per 100 PY of treatment. The corrected PI and PI for evaluable cycles excluded any treatment cycles where patients had no sexual activity or where additional contraceptive measures were used. A preplanned pooled analysis of Study 301 and 302 was conducted for the PI end points. Other outcomes of interest to this review were treatment acceptability, scheduled and unscheduled vaginal or uterine bleeding, and AEs.

Two trials were conducted in Europe (Study 301 and 302) and 1 study (Study 303) was conducted in the US. A total of 713, 858 and 1,006 patients received drospirenone for a median of 364, 252, and 168 days in Study 301, 302, and 303, respectively. The mean age of patients was 28.7 years (standard deviation [SD] = 7.1) and 28.9 years (SD = 7.1) in Study 301 and 302, respectively, and approximately 5% of patients had a body mass index (BMI) of 30 kg/m^2 or higher. In Study 303 the mean age was 27.5 years (SD = 5.9) and 35% of patients had a BMI of 30 kg/m^2 or higher.

Of note, no data from the desogestrel group in Study 302 were included in this report because this drug is not currently approved for use in Canada and is not a relevant comparator.

Efficacy Results

During Study 301, 3 pregnancies occurred over a total of 7,638 exposure cycles. The corrected PI was 0.54 pregnancies per 100 PY (95% CI, 0.11 to 1.59) and the overall PI was 0.51 (95% CI, 0.11 to 1.49). Study 302 reported 5 pregnancies over 6,691 exposure cycles. The corrected PI was 1.09 (95% CI, 0.35 to 2.54) and the overall PI was 0.97 (95% CI, 0.32 to 2.27). In both studies, all pregnancies occurred in patients who were 35 years of age or younger, and the PI results in this subgroup were generally similar to those reported for the overall study populations.

In the preplanned pooled analysis of Study 301 and 302, the corrected PI was 0.79 (95% CI, 0.31 to 1.56) and the overall PI for was 0.73 (95% CI, 0.31 to 1.43) for all drospirenone treated patients (N = 1,571; 14,329 cycles). For patients 35 years of age or younger (N = 1,251; 11,145 cycles), the pooled corrected PI was 1.02 (95% CI, 0.44 to 2.01), and the overall PI 0.93 (95% CI, 0.40 to 1.84).

In study 303, the efficacy analyses included 12 confirmed on-drug pregnancies that occurred over 6,566 exposure cycles in patients who were not breastfeeding (N = 993). The PI for evaluable cycles was 2.6 pregnancies per 100 PY (95% CI, 1.3 to 4.5) and the overall PI was 2.4 (95% CI, 1.2 to 4.2). In the subgroup of patients 35 years or younger, the PI for evaluable cycles was 2.9 (95% CI, 1.5 to 5.1) and the overall PI was 2.7 (95% CI, 1.4 to 4.7).

For acceptability, most patients in Study 301 rated their wellbeing during the intake of drospirenone as excellent (306 patients, 44%) or good (270 patients, 39%), with 52 patients (7%) rating wellbeing as moderate and 45 patients (6%) rating it as bad, at the last study visit. Patients who switched from another contraceptive, rated their wellbeing as better (127 patients, 33%), unchanged (172 patients, 44%) or worse (82 patients, 21%).

At the last study visit in Study 303, most patients strongly agreed (273 patients, 43%) or agreed (211 patients, 33%) that the contraceptive method was satisfactory, whereas 53 patients (8%) were undecided and 86 patients (14%) either disagreed or strongly disagreed. For those who switched from another contraceptive, more patients rated their wellbeing as better (156 patients, 31%), or unchanged (214 patients, 42%), with 74 patients rating as worse (14%).

Harms Results

Treatment-emergent AEs (TEAEs) were reported by 348 patients (49%), 332 patients (39%), and 614 patients (61%) in Study 301, 302, and 303, respectively. Across the trials, the most common TEAEs were headache (4% to 6%), nasopharyngitis (3% to 8%), acne (3% to 6%), breast pain (1% to 5%), nausea (0.3% to 6%), dysmenorrhea (0.3% to 6%) and metrorrhagia (0.3% to 5%). Overall, 10% to 12% of patients discontinued due to AEs, with bleeding-related events (3.3% to 4.2%), acne (0.8% to 2.9%) and weight increased (0.3% to 1.2%) being the most common reasons reported.

Serious TEAE were reported by 1.4% to 1.7% of patients enrolled in the trials. Serious hyperkalemia events were experienced by 4 patients in Study 303 (0.4%) and 1 patient in Study 302 (0.1%). No patients died during the studies.

No VTE AEs were reported in any of the studies, and a total of 5 patients (0.5%) in Study 303 and 1 patient (0.1%) in Study 302 experienced hyperkalemia.

The proportion of patients who discontinued drospirenone due menstruation or uterine bleeding-related TEAEs ranged from 3.3% to 4.2% across the 3 trials. The proportion of patients with bleeding or spotting that was scheduled (during hormone-free interval) and unscheduled (while taking active hormones) was highest in cycles 2 to 4, and generally decreased over time. In cycles 2 to 4, 68% to 76% of patients experienced unscheduled bleeding, and in the last follow-up period (cycles 7 to 9 in Study 302 and cycles 11 to 13 in Study 301 and 303), 52% to 65% reported unscheduled bleeding or spotting. As for the frequency of scheduled bleeding or spotting, 56% and 68% of patients reported bleeding in cycle 2 to 4, and 38% and 44% reported bleeding during cycles 11 to 13 in Study 303 and 301, respectively. Scheduled bleeding was not reported in Study 302.

Critical Appraisal

The key limitation of all studies was the lack of a relevant control group to inform the efficacy and safety of drospirenone versus other POP options available in Canada. In addition, Study 303 had a high withdrawal frequency, with only 35% of patients completing the 13-cycle study. Missing data were an issue for the acceptability outcomes (i.e., missing at the last study visit for 6% and 38% of patients in Study 301 and 303) and the proportion of patients with scheduled and unscheduled bleeding (i.e., missing for 30%, 56%, and 69% of patients at last follow-up period in studies 301, 302, and 303, respectively). Considering the losses to follow-up over time, it is unclear if the results are representative of the overall study population.

Overall, the clinical expert consulted for this review did not identify any major generalizability issues with the finding of the key clinical trials, even though there were some differences in regard to the distribution of age, BMI, race, and concurrent conditions in the study population relative to clinical practice in Canada. There was no efficacy data in patients who were breastfeeding, and all the studies excluded patients with specific comorbidities, such as cardiovascular, renal, or liver disease, diabetes with vascular involvement, psychiatric or substance use disorders, and those with a higher risk of VTE. Due to these exclusions, the safety and efficacy of drospirenone in patients with these conditions is unclear.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

For single-arm trials, although GRADE guidance is not available for noncomparative studies, the CADTH review team assessed pivotal single-arm trials for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for single-arm trials started at a very low certainty with no opportunity for rating up.

Study 302 was classified as a single-arm study in this report and for the GRADE assessment because the study's protocol did not define any hypotheses to be tested on the comparative efficacy of drospirenone versus desogestrel. Even though the study randomized patients to a treatment and control group, the efficacy outcomes were analyzed independently for each treatment group, as if they were from a single-arm trial.

For the GRADE assessments, findings from Study 301, 302, and 303 were considered together and summarized narratively per outcome because these studies were similar in population, interventions, design, and outcome measures. However, there was 1 exception to this approach. While the corrected PI and PI for evaluable cycles appear to measure the same concept (PI corrected for sexual activity without backup contraception), it was not clear that these end points were estimated using identical methods and thus the corrected PI in Study 301 and 302 was assessed separately from the PI for evaluable cycles in Study 303.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with a clinical expert and input received public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- corrected PI, PI for evaluable cycles, and overall PI
- acceptability
- scheduled and unscheduled bleeding or spotting
- discontinuation due to menstruation or uterine bleeding-related AEs
- hyperkalemia and VTE.

Based on input from the clinical expert, the GRADE assessment focused on the overall study populations (i.e., all age groups), as this was deemed the most generalizable to clinical practice and is consistent with the Health Canada indication.

The key comparator for the GRADE assessment was norethindrone, the only other POP approved for use in Canada.

Table 3: Summary of Findings for Drospirenone for Contraception Control in Adults (3 trials: Study 301, 302, and 303)

Outcome and follow-up	Patients (studies), N	Effect	Certainty[a]	What happens
Corrected PI				
PI (Pregnancies per 100 PY exposure) corrected for sexual activity and use of other contraceptives (95% CI) Follow-up: 9 or 13 cycles[b]	1,571 (2 single-arm trials)	Study 301: 0.54 (0.11 to 1.59) Study 302: 1.09 (0.35 to 2.54) **Pooled studies 301 and 302: 0.79 (0.31 to 1.56)**	Very low	The evidence is very uncertain about the effect of drospirenone on corrected PI when compared with any comparator.
PI for Evaluable cycles				
PI (Pregnancies per 100 PY exposure) for evaluable cycles with sexual activity and no use of other contraceptives (95% CI) Follow-up: 13 cycles	993 (1 single-arm trial)	Study 303: 2.6 (1.3 to 4.5)	Very low	The evidence is very uncertain about the effect of drospirenone on PI for evaluable cycles when compared with any comparator.
Overall PI				
Overall PI (Pregnancies per 100 PY exposure) (95% CI) Follow-up: 9 or 13 cycles[b]	2,564 (3 single-arm trials)	Study 301: 0.51 (0.11 to 1.49) Study 302: 0.97 (0.32 to 2.27) **Pooled studies 301 and 302: 0.73 (0.31 to 1.43)** Study 303: 2.4 (1.2 to 4.2)	Very low	The evidence is very uncertain about the effect of drospirenone on overall PI when compared with any comparator.
Acceptability				
Proportion of patients who responded to treatment acceptability questions Follow-up: 13 cycles	1,329 (2 single-arm trials)	**Study 301:** Most patients rated their wellbeing during the intake of drospirenone as excellent (44 per 100) or good (39 per 100), with 7 per 100 patients rating wellbeing as moderate and 6 per 100 rating it as bad. Patients who switched from another contraceptive, rated their wellbeing as better (33 per 100), unchanged (44 per 100), or worse (21 per 100). **Study 303:** Most patients strongly agreed (43	Very low[c]	The evidence is very uncertain about the effect of drospirenone on acceptability when compared with any comparator.

Outcome and follow-up	Patients (studies), N	Effect	Certainty[a]	What happens
		per 100) or agreed (33 per 100) that the contraceptive method was satisfactory, whereas 8 per 100 were undecided and 14 per 100 either disagreed or strongly disagreed. For those who switched from another contraceptive, patients rated their wellbeing as better (31 per 100), unchanged (42 per 100), or worse (14 per 100).		
Harms				
Patients with unscheduled bleeding or spotting[d]				
Proportion of patients with unscheduled bleeding or spotting Follow-up: 9 or 13 cycles[b]	1,770 (3 single-arm trials)	Study 301 (cycle 11 to 13): 640 per 1,000 Study 302 (cycles 7 to 9): 650 per 1,000 Study 303 (cycle 11 to 13): 520 per 1,000	Very low[c]	The evidence is very uncertain about the effect of drospirenone on unscheduled bleeding and/or spotting when compared with any comparator.
Patient with scheduled bleeding or spotting[e]				
Proportion of patients with scheduled bleeding or spotting Follow-up: 13 cycles	1,243 (2 single-arm trials)	Study 301 (cycle 11 to 13): 440 per 1,000 Study 303 (cycle 11 to 13): 380 per 1,000	Very low[c]	The evidence is very uncertain about the effect of drospirenone on scheduled bleeding or spotting when compared with any comparator.
Discontinuation due to menstruation or uterine bleeding-related adverse events				
Proportion of patients who discontinued due to bleeding-related TEAEs Follow-up: 9 or 13 cycles[b]	2,577 (3 single-arm trials)	Study 301: 42 per 1,000 Study 302: 33 per 1,000 Study 303: 39 per 1,000	Very low	The evidence is very uncertain about the effect of drospirenone on discontinuation due to bleeding or spotting when compared with any comparator.
Hyperkalemia				
Proportion of patients with hyperkalemia Follow-up: 9 or 13 cycles[b]	2,577 (3 single-arm trials)	Study 301: 0 per 1,000 Study 302: 1 per 1,000 Study 303: 5 per 1,000	Very low	The evidence is very uncertain about the effect of drospirenone on hyperkalemia when compared with any comparator.

Outcome and follow-up	Patients (studies), N	Effect	Certainty[a]	What happens
Venous thromboembolism				
Proportion of patients with VTE Follow-up: 9 or 13 cycles[b]	2,577 (3 single-arm trials)	No patients experienced VTE	Very low	The evidence is very uncertain about the effect of drospirenone on VTE when compared with any comparator.

CI = confidence interval; PI = Pearl Index; PY = person-year; TEAEs = treatment-emergent adverse event; VTE = venous thromboembolism.

Note: All serious concerns with study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, and publication bias are documented in the table footnotes.

PI is the number of pregnancies per 100 PY of exposure.

[a]In the absence of a comparator group, conclusions about efficacy relative to any comparator cannot be drawn and the certainty of evidence is started at very low and cannot be rated up.

[b]The study duration was 13 cycles for Study 301 and 303, and 9 cycles for Study 302.

[c]–1 level for serious risk of bias due to missing data (direction unclear).

[d]Scheduled bleeding day: any bleeding or spotting that occurs during hormone-free intervals (defined as days 25 to 28 +/− 1). Up to 8 consecutive bleeding or spotting days are considered as scheduled bleeding days.

[e]Unscheduled bleeding or spotting day: any bleeding or spotting that occurs while taking active hormones (days 2 to 23), except days which are classified as scheduled bleeding days.

Source: Clinical Study Report (CSR) for Study 301, CSR for Study 302, CSR for Study 303, Additional data supplied by Sponsor October 11, 2023.

Long-Term Extension Studies

Study 304, which reported on the safety of drospirenone among adolescents, was summarized in the section addressing gaps in the evidence of from the systematic review. No other long-term extension studies were submitted by the sponsor.

Indirect Comparisons

No indirect comparisons were submitted by the sponsor.

Studies Addressing Gaps in the Evidence From the Systematic Review

This section includes 1 additional relevant study, Study 304, that was included in the sponsor's submission to CADTH. Study 304 provides supportive evidence on vaginal bleeding pattern, withdrawal due to TEAEs, and acceptability for adolescent patients; that is for female adolescents aged 12 to 17 years, which was a patient group not included in Study 301, 302, and 303. Furthermore, the clinical expert consulted by CADTH stated that efficacy findings in adults would be generalizable to younger people. The CADTH review team summarized the study designs and data of Study 304 to provide supplemental evidence for decision-making.

Description of Studies

Study 304 was a multicentre, open-label, prospective, nonrandomized phase III trial of drospirenone 4 mg. Duration of study was 6 cycles plus an optional 7 cycle extension. This study was conducted in Germany, Finland, Sweden, and Ukraine and 103 female adolescents were allocated to treatment and received drospirenone 4 mg oral tablets using a 24/4-day regimen. The primary outcomes were vaginal bleeding pattern and withdrawal due to TEAEs.

Efficacy Results

Data on the acceptability of drospirenone was collected for the 13 cycles and summarized here based on the last nonmissing postbaseline study visit. A total of 100 patients provided responses to the acceptability questions. The rating of tolerability by patients reported as excellent (47.1%), good (35.3%), or moderate (15.7%). None of the patients rated tolerability as bad at any scheduled time point. In regard to bleeding patterns, the majority of patients considered that the treatment with drospirenone 4 mg positively affected the volume of vaginal bleeding during the cycle (greatly improved: 29.4%; improved: 46.1%; not changed: 17.6%; worsened: 4.9%), duration of vaginal bleeding (greatly improved: 25.5%; improved: 44.1%; not changed: 19.6%; worsened: 6.9%) and predictability of vaginal bleeding during the cycle (greatly improved: 12.7%; improved: 48.0%; not changed 17.6%; worsened 17.6%; greatly worsened 2%)

Harms Results

During the 13-cycle study, a trend toward less bleeding was observed over time. The proportion of patients with scheduled bleeding and/or spotting decreased from 77.5% during cycles 2 to 4 to 43.3% during cycles 11 to 13; that of unscheduled bleeding decreased from 73.0% to 61.2%. The median overall number of bleeding and/or spotting days decreased from 14.0 days in cycles 2 to 4 to 11.0 days in cycles 11 to 13. The median number of scheduled bleeding and/or spotting days decreased from 4.0 days in cycles 2 to 4 to 0.0 days in cycles 11 to 13. By contrast, the median number of unscheduled bleeding and/or spotting days fluctuated between 5.0 and 6.0 days during the first 3 reference periods and reached the maximum of 8.0 days during cycles 11 to 13.

For the overall (core and extension) study period 6% of patients stopped treatment due to abnormal bleeding, including 5 patients due to metrorrhagia and 1 due to amenorrhea.

For the overall (core and extension) study period, 63.7% of patients experienced at least 1 TEAE. The percentage of patients that experienced a serious TEAE was 2%. The percentage of patients that prematurely discontinued the trial due to TEAEs was 10.8%. The most frequently reported reason for discontinuation due to TEAEs was metrorrhagia in 4.9% of patients.

Critical Appraisal

Study 304 is an open-label and nonrandomized trial, and the estimates of efficacy are at risk of bias due to the lack of comparator estimated. The lack of blinding may affect patients' expectations of treatment and influence reporting of subjective measures such as acceptability or AEs.

The generalizability of the results to the population are limited in Canada, since the study population are from Germany, Finland, Sweden, and Ukraine only. Further, patients with specific comorbidities, psychiatric illness, specific BMI, alcohol abuse, and drug abuse were excluded from study. Due to these exclusions, the generalizability of the results to the individuals with those conditions is unclear.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	For conception control in females of reproductive potential
Treatment	Drospirenone
Dose regimen	One tablet daily
Submitted price	$10.99 per 28-day pack (one tablet per day)
Treatment cost	$143 annual cost
Comparator	Norethindrone (Jencycla, Movisse, Maeve)
Perspective	Publicly funded health care payer in Canada
Time horizon	One year
Key data source	Key assumption of equal treatment efficacy and safety of drospirenone and norethindrone was based on a naive comparison using published literature (i.e., editorial letter)
Costs considered	Drug acquisition costs
Submitted results	Incremental costs = $0 (annual treatment cost of drospirenone and norethindrone are both $143 per person)
Key limitations	The sponsor's assumption of comparable clinical efficacy and safety between drospirenone and norethindrone is uncertain because there was no direct or indirect comparative clinical evidence to support this assumption. Furthermore, the sponsor assumed that the only relevant comparator for drospirenone is progestin-only pills and did not include oral contraceptives other than norethindrone in the review. As such, the relative cost-effectiveness of drospirenone compared with oral contraceptives other than norethindrone is unknown. Importantly, there are other oral contraceptives available in Canada that are less costly than drospirenone.
CADTH reanalysis results	• CADTH did not undertake any reanalyses on the sponsor's cost-minimization analysis and highlights the uncertainty in the assumption of equal efficacy and safety. • If drospirenone is considered to be similar to norethindrone in safety and efficacy, then treatment with drospirenone should have no increase to drug plans budgets based on its submitted price relative to the published list price of norethindrone.

Budget Impact

CADTH noted that the use of a claims-based approach to estimate market size introduces uncertainty with the anticipated budget impact of drospirenone. CADTH did not conduct a base-case analysis, as the issues related to uncertainty in market size could not be addressed. The sponsor's base case suggested that there is no incremental budget associated with the reimbursement of drospirenone for contraception control in women of reproductive potential. These results assume no market displacement of any comparator other

than norethindrone, and equal pricing of drospirenone and norethindrone. If these assumptions are not true, reimbursement of drospirenone may lead to increased budget spending.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed.

Meeting date: January 24, 2024

Regrets: One expert committee member did not attend.

Conflicts of Interest: None

ISSN: 2563-6596

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