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CADTH Reimbursement Review

Drospirenone (Slynd)

Sponsor: Duchesnay Inc.
Therapeutic area: Oral contraceptive

Clinical Review
Pharmacoeconomic Review

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Clinical Review

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Abbreviations

BMI	body mass index
CI	confidence interval
COC	combined oral contraceptive
CPPS	core per-protocol set
FAS	full analysis set
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IUD	intrauterine device
PI	Pearl Index
POP	progestin-only contraceptive
PPS	per-protocol set
PY	person-years
RCT	randomized controlled trial
SD	standard deviation
TEAE	treatment-emergent adverse event
VTE	venous thromboembolism

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Background Information of Application Submitted for Review

Item	Description
Drug product	Drospirenone (Slynd), 4 mg tablet; oral administration
Sponsor	Duchesnay Inc.
Indication	For conception control in adolescent and adult females
Reimbursement request	As per indication
Health Canada approval status	Approved (NOC granted)
Health Canada review pathway	Standard
NOC date	November 30, 2021
Recommended dosage	Drospirenone 4 mg daily on days 1 to 24, followed by 1 inert tablet on days 25 to 28

NOC = Notice of Compliance.

Source: Sponsor submission.[1]

Introduction

Unintended pregnancies are those that are either unwanted (occurring when no or no more children are desired) or mistimed (occurring earlier than desired).[2] Most unintended pregnancies are a result of not using contraception (i.e., birth control, or using it inconsistently or incorrectly.[2] The Society of Obstetricians and Gynecologists of Canada states that nearly 50% of all pregnancies in Canada are unintended.[3] The annual number of unintended pregnancies in Canada among females aged 18 to 44 years was estimated at 180,733 in 2015, with 58% occurring in females aged between 20 and 29 years.[4] Imperfect use of contraception use accounted for 69% and 82% of annual unintended pregnancies in females aged 18 to 44 years and 20 to 29 years, respectively.[4] Unintended pregnancies among females in Canada were associated with maternal sociodemographic factors such as age, immigration status, level of education, presence of a partner, experience of violence, past pregnancy, smoking, and use of alcohol or drugs before pregnancy.[5]

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, and injectables). The currently available and reimbursed POPs in Canada all contain 0.35 mg of norethindrone.[6-8] Norethindrone may be used by most females, including those for whom estrogen is contraindicated or less appropriate, such as those who are lactating.[9,10] However, norethindrone 0.35 mg daily does not reliably inhibit ovulation, and must be administered at precisely the same time each day.[8,11] Use of back-up contraception is recommended for patients who have missed a dose by more than 3 hour.[8] POPs are also associated with unpredictable and irregular bleeding, which is a common reason for discontinuation.[11] With POPs, interpreting the signs and symptoms of pregnancy may be difficult due the frequency of unscheduled bleeding and spotting.[11]

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of drospirenone 4 mg oral tablets for conception control in adolescent and adult females.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from a clinical expert consulted by CADTH for the purpose of this review.

Patient Input

No patient input was received.

Clinician Input

Input From the 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. 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 and improved convenience, and offer 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 those who are breastfeeding. The expert anticipated that drospirenone will shift the treatment paradigm for those who require an oral progestin-only contraceptive, and it will have widespread and relevant use for its noncontraceptive benefits in the management of abnormal uterine bleeding and endometriosis, and 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 effects in adults and adolescents because these patients are considered hormonally similar.

Clinician Group Input

No clinician group input was received.

Drug Program Input

The drug programs identified issues related to relevant comparators, considerations for initiation and prescribing of therapy, generalizability, and systemic and economic issues (Table 4).

Clinical Evidence

Systematic Review

Description of Studies

The systematic review included 3 studies of drospirenone in adult females at risk of pregnancy. The primary objective of the trials was to demonstrate the contraceptive efficacy of drospirenone, and the secondary objectives were to demonstrate safety and tolerability. Study 301 and Study 303 were open-label, noncomparative, phase III trials in which 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 nine 28-day cycles or desogestrel 0.075 mg daily. The primary and secondary efficacy outcomes of interest to this review were the overall Pearl Index (PI), the corrected PI, and the PI for evaluable cycles for the drospirenone treatment groups. The PI is the number of pregnancies per 100 person-years (PYs) of treatment. The corrected PI and PI for evaluable cycles excluded any treatment cycles during which patients had no sexual activity or additional contraceptive measures were used. A preplanned pooled analysis of Study 301 and Study 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 adverse events.

Two trials were conducted in Europe (Study 301 and Study 302) and 1 (Study 303) was conducted in the US. Totals of 713, 858, and 1,006 patients received drospirenone for a median of 364, 252, and 168 days in Study 301, Study 302, and Study 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 Study 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.

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

Efficacy Results

During Study 301, investigators reported 3 pregnancies occurred over a total of 7,638 exposure cycles. The corrected PI was 0.54 pregnancies per 100 PYs (95% confidence interval [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 aged 35 years 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 Study 302, the corrected PI was 0.79 (95% CI, 0.31 to 1.56) and the overall PI was 0.73 (95% CI, 0.31 to 1.43) for all patients treated with drospirenone (N = 1,571; 14,329 cycles). For patients aged 35 years 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 was 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 PYs (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).

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

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

Harms Results

Treatment-emergent adverse events (TEAEs) were reported by 348 patients (49%), 332 patients (39%), and 614 patients (61%) in Study 301, Study 302, and Study 303, respectively. Across the trials, the most common TEAEs were headaches (reported by 4% to 6% of patients), 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 adverse events, with bleeding-related events (3.3% to 4.2%), acne (0.8% to 2.9%) and increased weight (0.3% to 1.2%) being the most common reasons reported.

Serious TEAEs 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 venous thromboembolism (VTE) adverse events 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%. The proportion of patients with bleeding or spotting that was scheduled (during hormone-free intervals) and unscheduled (while taking active hormones) was highest in cycle 2 to 4, and generally decreased over time. In cycle 2 to 4, 68% to 76% of patients experienced unscheduled bleeding, and in the last follow-up period (cycle 7 to 9 in Study 302 and cycle 11 to 13 in Study 301 and Study 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 cycle 11 to 13 in Study 303 and Study 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 affected the acceptability outcomes (i.e., data for 6% and 38% of patients were missing at the last study visit in Study 301 and Study 303, respectively) and the proportion of patients with scheduled and unscheduled bleeding (i.e., missing for 30%, 56%, and 69% of patients at the last follow-up period in Study 301, Study 302, and Study 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 findings of the key clinical trials, despite some differences in the distributions of age, BMI, race, and concurrent conditions in the study population relative to Canadian clinical practice. There were no efficacy data in patients who were breastfeeding, and all the studies excluded patients with specific comorbidities (e.g., cardiovascular, renal, or liver disease; diabetes with vascular involvement; or 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, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for those outcomes most relevant to inform the deliberations of CADTH's expert committee, and a final certainty rating was determined as outlined by the GRADE Working Group.[12,13]

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. Because the lack of a comparator arm precludes drawing conclusions about the effect of the intervention versus any comparator, the certainty of evidence for single-arm trials started at 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. Although the study randomized patients to treatment and control groups, the efficacy outcomes for each treatment group were analyzed independently, as if they were from a single-arm trial.

For GRADE assessments, the findings from Study 301, Study 302, and Study 303 were considered together and summarized narratively according to 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 the PI for evaluable cycles appear to measure the same concept (PI corrected for sexual activity without back-up contraception), it was not clear that these end points were estimated using identical methods. The corrected PIs in Study 301 and Study 302 were therefore 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 members of the expert committee:

- corrected PI, PI for evaluable cycles, and overall PI
- acceptability
- scheduled and unscheduled bleeding or spotting
- discontinuation due to menstruation or uterine bleeding–related adverse events
- 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, which is the only other POP approved for use in Canada.

Table 2: Summary of Findings for Drospirenone for Conception Control in Adults (Study 301, Study 302, and Study 303)

Outcome and follow-up	Patients, N (studies)	Effect	Certainty[a]	What happens
Corrected PI (95% CI)				
PI (pregnancies per 100 PYs of exposure) corrected for sexual activity and use of other contraceptives 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 (95% CI)				
PI (pregnancies per 100 PYs of exposure) for evaluable cycles with sexual activity and no use of other contraceptives 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 (95% CI)				
Overall PI (pregnancies per 100 PYs of exposure) 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

Outcome and follow-up	Patients, N (studies)	Effect	Certainty[a]	What happens
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 well-being during the intake of drospirenone as excellent (44 per 100) or good (39 per 100), with 7 per 100 patients rating well-being as moderate and 6 per 100 rating it as bad Patients who switched from another contraceptive rated their well-being as better (33 per 100), unchanged (44 per 100) or worse (21 per 100) **Study 303:** Most patients strongly agreed (43 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 well-being as better (31 per 100), unchanged (42 per 100), or worse (14 per 100)	Very low[c]	The evidence is very uncertain about the effect of drospirenone on acceptability when compared with any comparator
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

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

CI = confidence interval; PI = Pearl Index; PY = person-year; TEAE = treatment-emergent adverse event.

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 PYs 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 started at very low and cannot be rated up.

[b]The study durations were 13 cycles for Study 301 and Study 303 and 9 cycles for Study 302.

[c]Rated down 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 day 25 to 28 ± 1). Up to 8 consecutive bleeding or spotting days are considered scheduled bleeding days.

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

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] and Clinical Study Report for Study 303.[16] Additional data supplied by sponsor, October 11, 2023.[17]

Long-Term Extension Studies

Study 304, which reported on the safety of drospirenone among adolescents, is summarized in the section addressing gaps in the evidence 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, which was included in the sponsor's submission to CADTH. Study 304 provides supportive evidence on vaginal bleeding patterns, withdrawal due to TEAEs, and acceptability for adolescent patients, i.e., females aged 12 to 17 years, which was a patient group not included in Study 301, Study 302, or Study 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. The duration of the study was 6 cycles plus an optional 7-cycle extension. This study was conducted in Germany, Finland, Sweden, and Ukraine. A total of 103 female adolescents were allocated to treatment and received 4 mg oral tablets daily using a regimen of 24 days of drospirenone tablets followed by 4 days of inert tablets. The primary outcomes were vaginal bleeding patterns and withdrawal due to TEAEs.

Efficacy Results

Data on the acceptability of drospirenone was collected for the 13 cycles is summarized here based on the last nonmissing postbaseline study visit. A total of 100 patients provided responses to the acceptability questions. Patients rated the tolerability of the drug as "excellent" (47.1%), "good" (35.3%), or "moderate" (15.7%). None of the patients rated the tolerability as "bad" at any scheduled time point. With regard to bleeding patterns, the majority of patients reported that 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%), the duration of vaginal bleeding (greatly improved: 25.5%; improved: 44.1%; not changed: 19.6%; worsened: 6.9%) and the 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 cycle 2 to cycle 4 to 43.3% during cycle 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 in cycle 2 to cycle 4 to 11.0 in cycle 11 to cycle 13. The median number of scheduled bleeding and/or spotting days decreased from 4.0 in cycle 2 to cycle 4 to 0.0 in cycle 11 to cycle 13. By contrast, the median number of unscheduled bleeding and/or spotting days fluctuated between 5.0 and 6.0 during the first 3 reference periods and reached the maximum of 8.0 during cycle 11 to cycle 13.

For the overall (core and extension) study period, 6% of patients stopped treatment due to abnormal bleeding: 5 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 who experienced a serious TEAE was 2%. The percentage of patients who

prematurely discontinued the trial due to TEAEs was 10.8%. The most frequently reported reason for discontinuation due to a TEAE was metrorrhagia, which was report by 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 a comparator. A lack of blinding may affect patients' expectations of treatment and influence reporting of subjective measures such as acceptability or adverse events.

The generalizability of the results to the Canadian population is limited, as the study populations are from Germany, Finland, Sweden, and Ukraine only. Patients with specific comorbidities, psychiatric illness, specific BMIs, alcohol abuse, or drug abuse were excluded from study. The generalizability of the results to individuals with those specific conditions is therefore unclear.

Conclusions

Three clinical trials (Study 301, Study 302, and Study 303) in adult females at risk of pregnancy demonstrated the contraceptive efficacy of drospirenone 4 mg over 1 year. This finding was based on overall PI and the PI results corrected for sexual activity without back-up contraception that met predetermined therapeutic thresholds for contraceptive efficacy set out by regulatory agencies. During the trials, the majority of patients reported unscheduled vaginal bleeding or spotting. Less than 5% of patients withdrew due to bleeding-related adverse events. No VTE events were reported in the trials, and hyperkalemia TEAEs were infrequent. A supplemental uncontrolled clinical trial in adolescents detected no new safety signals after up to 1 year of drospirenone treatment.

No indirect treatment comparison for drospirenone versus norethindrone was submitted by the sponsor. Given the lack of direct or indirect comparative evidence involving a relevant comparator, no conclusions can be drawn about the efficacy and safety of drospirenone relative to other POPs available in Canada.

Introduction

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of drospirenone 4 mg oral tablets for conception control in adolescent and adult females.

Disease Background

The contents within this section were informed by materials submitted by the sponsor and clinical expert input. The following summary was validated by the CADTH review team.

Unintended pregnancies are those that are either unwanted (occurring when no or no more children are desired) or mistimed (occurring earlier than desired).[2] Most of the unintended pregnancies are a result of not using contraception (birth control) or using it inconsistently or incorrectly.[2] Unintended pregnancies among females in Canada are associated with maternal sociodemographic factors, such as age, immigration status,

level of education, presence of a partner, experience of violence, past pregnancy, smoking, and use of alcohol or drugs before pregnancy.[5]

The Society of Obstetricians and Gynecologists of Canada states that nearly 50% of all pregnancies in Canada are unintended.[3] The prevalence of females of reproductive age (15 to 49 years) in Canada was estimated at 8,773,720 in 2022.[18] The annual number of unintended pregnancies in Canada among females aged 18 to 44 years was estimated at 180,733 in 2015, with 58% occurring in females aged between 20 and 29 years.[4] Imperfect contraceptive use accounted for 69% and 82% of annual unintended pregnancies in females aged 18 to 44 years and 20 to 29 years, respectively.[4]

Unintended pregnancies account for the majority of induced abortions.[19] Based on data available from the Canadian Institute for Health Information, 74,155 and 87,485 induced abortions were reported in 2020 and 2021, respectively.[20] In 2020, approximately 2.5% of all induced abortions in Canada were associated with complications such as hemorrhage, infection, and retained products of conception (i.e., placental and/or fetal tissue that remains in the uterus).[20]

Standards of Therapy

The contents in this section were informed by materials submitted by the sponsor and clinical expert input. The following summary was validated by the CADTH review team.

The goal of contraception is to provide effective and reliable prevention of pregnancy using a method that is reversible and allows for rapid return to fertility once the contraceptive is discontinued. The ideal treatment should be easy for patients to access and adhere to and have minimal adverse effects.[21] While a wide selection of contraceptives are reimbursed by public health care plans in Canada, oral contraceptives are the most popular.[10]

Various types of hormonal and nonhormonal contraceptive options are currently recommended in Canada, including both long-acting reversible contraceptives (IUDs and implants) and short-acting reversible contraceptives (COCs, POPs, transdermal patches, vaginal rings, and injectables).The choice of a contraceptive must consider safety, effectiveness, accessibility, affordability, and acceptability.[21] Some data suggest that, while efficacy is important, it may not always be the only, or the most important, factor when patients make decisions about contraception.[22] Respondents to a survey rated the following characteristics of contraceptive methods as “extremely” important: very effective at preventing pregnancy (89% of respondents); easy to use (80%); few or no adverse effects (74%); control over when and whether to use the method (71%); no one can tell that the method is being used (55%); no change in menstrual periods (44%).[22]

The currently available and reimbursed POPs in Canada (Jencycla, Movisse, and Maeve) all contain 0.35 mg of norethindrone.[6-8] They are supplied in packages of 28 tablets with no hormone-free intervals.[6-8] Norethindrone may be used by most females, including those for whom estrogen is contraindicated or considered less appropriate, such as lactating females.[9,10] However, norethindrone 0.35 mg daily does not reliably inhibit ovulation, and functions as a contraceptive through other mechanisms, such as action on the cervical mucus, endometrial receptivity, and tubal ciliary motility.[11] Norethindrone should be administered at the same time each day, with a missed-pill window of only 3 hours.[8] The use of back-up contraception

is recommended for 48 hours if patients miss a dose by more than 3 hours.[8] POPs are also associated with unpredictable and irregular bleeding, which is a common reason for discontinuation.[11] With POPs, interpreting signs and symptoms of pregnancy may be difficult, due to the frequency of unscheduled bleeding and spotting.[11]

In youth, it is estimated that 95% of sexually active adolescents who are not using contraception will become pregnant within 1 year.[23] For adults, the estimate is 85%.[24] For oral contraceptive pills, COCs, and POPs, it is estimated that 0.3% to 1% of patients will become pregnant in the first year if contraceptives are used perfectly (i.e., consistently and correctly), and 9% will become pregnant with typical use.[24]

Drug Under Review

Drospirenone is a progestin-only tablet with no estrogen component, and is indicated for conception control in adolescent and adult females.[25] Drospirenone is formulated as 24 tablets of 4 mg drospirenone and 4 inert tablets for oral administration once daily for 28 consecutive days. The first active white tablet should be taken on the first day of menses and thereafter once daily at the same time each day for a total of 24 days. For the 4 remaining days, 1 green inert tablet should be taken daily.[25]

Drospirenone is a spironolactone analogue with antimineralocorticoid activity that lowers the risk of becoming pregnant primarily by suppressing ovulation.[25]

Health Canada issued a Notice of Compliance for drospirenone as a POP on November 30, 2021. The sponsor requested reimbursement for drospirenone as indicated for conception control in adolescent and adult females.[1] Drospirenone as a POP has not been previously reviewed by CADTH, but an oral contraceptive containing drospirenone in combination with ethinyl estradiol was assessed by CADTH in 2005.

Key characteristics of drospirenone are summarized in Table 3 along with those of the other progestin-only oral contraceptives available in Canada.

Table 3: Key Characteristics of Drospirenone and Norethindrone

Characteristic	Drospirenone	Norethindrone
Mechanism of action	Suppressing ovulation	Pelvic effects include changes in the cervical mucus and endometrium; systemic effects involve mainly the inhibition of secretion of pituitary gonadotrophins, which in turn prevents follicular maturation and ovulation
Indication[a]	Conception control in adolescent and adult females	Conception control
Route of administration	Oral	Oral
Recommended dose	One tablet daily for 28 consecutive days following a 24/4 regimen (24 white tablets containing 4 mg of drospirenone, and 4 green inert tablets) **Missed dose:** If 1 white active tablet is missed, take the missed tablet as soon as	One tablet daily for 28 consecutive days (based on 28-day regimen); each tablet contains 0.35 mg norethindrone **Missed dose:** If a patient is more than 3 hours late taking their progestin-only pill, they should take the missed pill as soon as they remember

Characteristic	Drospirenone	Norethindrone
	possible; continue taking 1 tablet a day until the pack is finished; back-up contraception is not required Based on a pharmacodynamics study that covered only 2 cycles, if 1 pill is missed occasionally, ovulation suppression is maintained	then go back to taking progestin-only pills at their regular time; a back-up method such as condoms and spermicides should be used for the next 48 hours whenever a progestin-only oral contraceptive is taken 3 or more hours late
Serious adverse effects or safety issues	Contraindicated in females with: • hypersensitivity to this drug or to any ingredient • renal impairment • adrenal insufficiency • presence or history of cervical cancer or progestin sensitive cancers • liver tumours, benign or malignant, or hepatic impairment • undiagnosed abnormal uterine bleeding	Progestin-only pills should not be used by females who currently have the following conditions: • when pregnancy is suspected or diagnosed • active liver disease or history of or actual benign or malignant liver tumours • known or suspected carcinoma of the breast • undiagnosed abnormal vaginal bleeding • hypersensitivity to any component of this product

[a]Health Canada–approved indication.

Sources: Drospirenone product monograph,[25] Jencycla product monograph,[8] Movisse product monograph,[7] and Maeve product monograph.[6]

Stakeholder Perspectives

Patient Group Input

No patient group submitted input to CADTH.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in conception control in adolescents and adults.

Unmet Needs

The clinical expert consulted by CADTH noted that contraception should be safe, accessible, affordable, reliable, effective, easy to use, and reversible. The expert stated 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 and improved convenience, and offer 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.

Place in Therapy

According to the clinical expert, drospirenone may be used by most patients, including those who cannot tolerate estrogen-containing therapies or who are breastfeeding. As a progestin-only method, the expert anticipated it will have wide and relevant use for noncontraceptive benefits in the management of abnormal uterine bleeding and endometriosis, and for its antiandrogenic properties.

The expert anticipated that drospirenone will shift the treatment paradigm for those who require an oral progestin-only contraceptive. The expert noted that drospirenone requires a less-strict administration schedule compared with other POPs, and back-up contraception is not required if 1 pill is missed.

The expert described drospirenone as an appropriate first-line therapy, and noted that it would not be necessary for patients to try other medications before initiating this therapy. The expert anticipated that drospirenone would replace neither estrogen-containing contraceptives, which are associated with less spotting and offer some noncontraceptive benefits (e.g., improved cycle control, reduction of acne, and reduction in ovarian cysts) related to estrogen, nor implants and IUDs, which are usually chosen for their effectiveness, longevity, and independence from the user once placed.

Patient Population

The expert stated that drospirenone is most suitable for those with contraindications to estrogen, those who failed previous use of estrogen-based therapies, and those who are breastfeeding, but it may also be used by other patients. 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 a similar treatment effect in adults and adolescents because these patients are hormonally similar.

Discontinuing Treatment

According to the clinical expert, choosing to discontinue drospirenone would require deciding if the patient needs an alternative therapy to control contraception, menstruation, or endometriosis. Adverse effects can be considered in choosing alternative contraceptives.

Prescribing Considerations

The expert stated that this medication could safely be prescribed by both primary care physicians and specialists.

Clinician Group Input

No clinician group provided input to CADTH.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may affect their ability to implement a recommendation. The

implementation questions and corresponding responses from the clinical expert consulted by CADTH are summarized in Table 4.

Table 4: Summary of Drug Plan Input and Clinical Expert Responses

Drug program implementation questions	Clinical expert response
Relevant comparators	
The clinical trials were prospective, multicentre, noncomparative studies. The authors suggested that the POP, drospirenone, would have comparable efficacy to COCs (e.g., Yaz) that contain a combination of drospirenone and estrogen. The drug plans noted that drospirenone may displace norethindrone as a POP. Drospirenone has a 24-hour window for late doses compared to norethindrone, which has a 3-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)?	Norethindrone is the most relevant comparator to drospirenone. Drospirenone can be expected to largely replace norethindrone, because in the clinical expert's opinion, drospirenone is likely more effective. Drospirenone is not anticipated to replace COC use, as these have some noncontraceptive benefits related to the estrogen, and are associated with less spotting than POPs.
Considerations for initiation of therapy	
Could experts see this medication being prescribed independent of its contraceptive effects (e.g., antiandrogenic affects — reduce acne, decrease hirsutism)? Is there potential for off-label use of drospirenone for noncontraceptive indications?	Drospirenone may be used off-label for its antiandrogenic properties and for the management of abnormal uterine bleeding and endometriosis care.
The drug plans note that all other contraceptives are open benefit.	Comment to inform CDEC deliberations.
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 of hormone-free tablets.	Comment to inform CDEC deliberations.
Generalizability	
In 2 of the clinical trials, > 99% of females 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 females in Canada have a BMI > 30 kg/m^2. A third clinical trial enrolled a population that was more racially diverse, with 35% of patients with 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?	No substantial concerns have been raised 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 the 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	Comments to inform CDEC deliberations.

Drug program implementation questions	Clinical expert response
share in 3 years. Drug plans stated that they prefer reduced cost as opposed to restrictions to obtain value.	

BMI = body mass index; CDEC = Canadian Drug Expert Committee; COC = combined oral contraceptive; POP = progestin-only pill.

Clinical Evidence

The objective of CADTH's Clinical Review Report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of drospirenone 4 mg oral tablets for conception control in adolescent and adult females. The focus will be placed on comparing drospirenone to relevant comparators and identifying gaps in the current evidence.

A summary of the clinical evidence included by the sponsor in the review of drospirenone is presented in 2 sections, with CADTH's critical appraisal of the evidence included at the end of each section. The first section, the systematic review, includes pivotal studies and RCTs that were selected according to the sponsor's systematic review protocol. CADTH's assessment of the certainty of the evidence in this first section using the GRADE approach follows the critical appraisal of the evidence. The second section includes additional studies that were considered by the sponsor to address important gaps in the systematic review evidence.

Included Studies

Clinical evidence from the following are included in the CADTH review and appraised in this document:

- 3 pivotal studies or RCTs identified in the systematic review (Study 301, Study 302, and Study 303)
- 1 additional study addressing gaps in evidence (Study 304), including the extension period for this trial.

No indirect evidence or other extension studies were submitted by the sponsor. The sponsor submitted Study 205, a single-centre, open-label, uncontrolled study (N = 21), which had as a primary objective as assessment of the safety of drospirenone on the endometrium.[26] According to the sponsor's systematic review protocol, this study did not meet the study design criteria (neither an RCT nor a pivotal study). As endometrial change was not an outcome of interest according to the clinical expert consulted by CADTH, nor was it an outcome specified in the sponsor's systematic review protocol, Study 205 was not summarized in this report.

The sponsor selected norethindrone as the key comparator in its systematic review protocol. The clinical expert consulted by CADTH and the CADTH review team agreed that this was the most relevant comparator in Canada. The only RCT submitted compared drospirenone to desogestrel, a progestin-only contraceptive that is not approved for use in Canada. Because desogestrel is not a relevant comparator, no data from this treatment group have been included in the CADTH clinical review.

Systematic Review

The contents within this section were informed by materials submitted by the sponsor. The following summary was validated by the CADTH review team.

Description of Studies

Characteristics of the included studies are summarized in Table 5. Studies 301 and 303 were considered pivotal trials by Health Canada, while Study 302 provided supportive evidence.

Study 301 was an open-label, multicentre, noncomparative, phase III trial of drospirenone administered for 13 cycles of 28 days each. The primary objective was to demonstrate contraceptive efficacy, and the secondary objective was to demonstrate the safety and tolerability of drospirenone. This study enrolled healthy females at risk of pregnancy between the ages of 18 and 45 years. All patients received drospirenone in a 28-day cycle that consisted of drospirenone 4 mg daily for 24 days followed by inert tablets for 4 days. A total of 724 patients were allocated to treatment. These patients were recruited in 41 centres in Czechia (i.e., the Czech Republic), Germany, Hungary, Poland, and Romania.

Study 302 was a multicentre, double-blind, double-dummy, randomized phase III trial in which patients were randomized to receive either drospirenone or desogestrel for nine 28-day cycles. Its primary objective was to demonstrate the contraceptive efficacy of drospirenone, and its secondary objective was to assess the safety and tolerability of drospirenone 4 mg administered in a 24-plus-4–day cycle in comparison to desogestrel 0.075 mg daily. This study enrolled females without uncontrolled current diseases at risk of pregnancy, between the ages of 18 and 45 years, with a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg. Treatment-group assignment was planned to occur at a 5:2 ratio and was conducted using via a centre-based automated blocking methodology. A total of 1,213 patients were randomized (872 to the drospirenone group and 341 to the desogestrel group). The trial was conducted in 73 centres in Austria, Czechia (i.e., the Czech Republic), Germany, Hungary, Poland, Romania, Slovakia, and Spain.

Study 303 was a multicentre, open-label, noncontrolled, phase III trial. Its primary objective was to demonstrate the contraceptive efficacy of drospirenone, and its secondary objective was to assess the safety, tolerability, and pharmacokinetics of drospirenone 4 mg for 13 cycles of the 28-day regimen. This study included postmenarcheal and premenopausal female patients aged 15 years and older who presented to the clinic seeking contraception. A total of 1,006 patients were enrolled in 39 trial centres in the US.

Populations

Inclusion and Exclusion Criteria

All 3 studies enrolled females who were willing to use the study drug as the sole contraceptive for the duration of the trials. The European studies limited entry to patients who were 18 to 45 years of age, while the US study allowed premenopausal females 15 years and older to enter. Study 303 included patients who were breastfeeding, while Study 301 and 302 excluded these patients. All patients were assessed for the risk of VTE based on family history, comorbid vascular or metabolic disease, body weight, age, and smoking status. Patients with an unfavourable VTE risk-versus-benefit ratio were not included in the studies. Patients

were also excluded if they had significant comorbid medical conditions; abnormal findings on pelvic, breast, ultrasound or Papanicolaou (Pap) screening; abnormal uterine bleeding or a bleeding disorder; a history of alcohol or drug abuse; or a psychiatric illness or suicide risk.

Table 5: Details of Studies Included in the Systematic Review

Detail	Study 301	Study 302	Study 303
Designs and populations			
Study design	Nonrandomized single-arm, open-label, phase III trial	Double-blind, active-controlled, phase III, RCT	Nonrandomized single-arm, open-label, phase III trial
Locations	41 sites in 5 countries (Czech Republic, Germany, Hungary, Poland, and Romania)	73 sites in 7 countries (Czech Republic, Germany, Hungary, Poland, Romania, Slovakia, and Spain)	39 sites in the US
Patient enrolment dates	**Start date:** July 11, 2011 **End date:** March 18, 2023	**Start date:** August 1, 2012 **End date:** January 27, 2014	**Start date:** October 9, 2014 **End date:** October 4, 2017
Enrolled or randomized (N)	724	1,213 Drospirenone: 872 Desogestrel: 341	1,006
Inclusion criteria	Healthy female at risk of pregnancy aged 18 to 45 years: • SBP < 140 mm Hg, DBP < 90 mm Hg • Patient agrees to use only study drug for contraception for at least 13 cycles • Menstruation restarted since last pregnancy (only applicable for females that were pregnant) • At least 4 menstrual cycles during the last 6 months were regular (i.e., cycle length between 24 and 35 days) for those without a recent history of hormonal contraceptive use (i.e., medication starters)	Female without uncontrolled current diseases at risk of pregnancy aged 18 to 45 years: • SBP < 140 mm Hg, DBP < 90 mm Hg • Patient agrees to use only study drug for contraception for at least 9 cycles • Menstruation restarted since last pregnancy (only applicable for females that were pregnant within the last 6 months) • At least 4 menstrual cycles during the last 6 months before study were regular (i.e., cycle length between 24 and 35 days) for those without a recent history of hormonal contraceptive use (i.e., starters)	Sexually active, postmenarcheal, and premenopausal female patients at risk of pregnancy including females aged 15 years and older who were breastfeeding: • SBP ≤ 159 mm Hg and DBP ≤ 99 mm Hg • Willing to use trial contraception for 13 cycles • Willing to have intercourse in each cycle of trial without the need to use back-up contraceptive • At least 3 complete menstrual cycles after delivery (only applicable for females who were pregnant within the last 6 months)[a] • Regular cycles during the last 6 months when not using hormonal contraception

Detail	Study 301	Study 302	Study 303
Exclusion criteria	• Pregnant or breastfeeding • Abnormal finding on pelvic, breast or ultrasound examination • Unexplained amenorrhea, polycystic ovary syndrome • ASC-US or more severe finding on Pap smear • Significant cardiovascular, hepatic or renal disease, diabetes with vascular involvement, uncontrolled thyroid disorder or current venous thrombosis or embolism • Evidence or history of alcohol, medication or drug abuse (within the last 12 months); neurotic personality, psychiatric illness or suicide risk • Known bleeding disorder or history of unexplained bleeding or bruising within the last 12 months • Prohibited previous or concomitant medicationb • Regular concomitant use of barrier or other contraceptive measures (excepting occasional use due to risk of infection)	• Pregnant or breastfeeding • Abnormal finding on pelvic, breast or ultrasound examination • Unexplained amenorrhea, polycystic ovary syndrome • Undiagnosed vaginal bleeding • ASC-US or more severe finding on Pap smear • Known or suspected sex-steroid–sensitive malignancies • Significant cardiovascular, hepatic, or renal disease; diabetes with vascular involvement; uncontrolled thyroid disorder; or current venous thrombosis or embolism • Evidence or history of alcohol, medication or drug abuse (within the last 12 months); neurotic personality, psychiatric illness or suicide risk • Known bleeding disorder or history of unexplained bleeding or bruising within the last 12 months • Prohibited previous or concomitant medicationc • Regular concomitant use of barrier or other contraceptive measures (excepting occasional use due to risk of infection)	• Pregnant • History of infertility (patient or male partner) • Abnormal finding on pelvic, breast or ultrasound examination • Unexplained amenorrhea, polycystic ovary syndrome • Undiagnosed genital bleeding • ASC-US or more severe finding on Pap smear • Known or suspected sex-steroid–sensitive malignancies, breast cancer • HIV or hepatitis infection • Significant cardiovascular, hepatic, or renal disease; diabetes with vascular involvement; or uncontrolled thyroid disorder • Headaches with focal neurologic symptoms • Current venous thrombosis or embolism; inherited or acquired predisposition to thromboembolism or bruising within the last 12 months • Evidence or history of alcohol, medication or drug abuse (within the last 12 months); clinically significant psychiatric illness or suicide risk • Prohibited previous or concomitant medicationd • Regular concomitant use of barrier or other contraceptive measures (excepting occasional use due to risk of infection)
Drugs			
Intervention	Drospirenone oral tablet using a 24-plus-4–day regimen:	Drospirenone oral tablet using a 24-plus-4–day regimen:	Drospirenone oral tablet using a 24-plus-4–day regimen:

Detail	Study 301	Study 302	Study 303
	• Day 1 to 24: drospirenone 4 mg • Day 25 to 28: inert tablets	• Day 1 to 24: drospirenone 4 mg • Day 25 to 28: inert tablets	• Day 1 to 24: drospirenone 4 mg • Day 25 to 28: inert tablets
Comparator	None	Desogestrel oral tablet 0.075 mg daily	None
Study duration			
Treatment phase	13 cycles of 28 days	9 cycles of 28 days	13 cycles of 28 days
Follow-up phase	10 to 28 days	7 to 10 days	10 to 14 days
Outcomes			
Primary end point	Overall PI	Overall PI	PI from evaluable cycles in females aged ≤ 35 years (at time of trial enrolment) who were not breastfeeding
Secondary and exploratory end points	**Secondary:** • PI for method failures • PI after correction for additional contraception and sexual activity • Pregnancy ratio **Exploratory:** • Acceptability **Safety and tolerability:** • Vaginal bleeding patterns • Harms	**Secondary:** • PI for method failures • PI after correction for back-up contraception and sexual intercourse status • Overall pregnancy ratio • Method failure pregnancy ratio **Safety and tolerability:** • Vaginal bleeding patterns • Harms	**Secondary:**[e] • Overall PI based in females aged ≤ 35 years • PI for method failures in females aged ≤ 35 years • Pregnancy ratio in females aged ≤ 35 years • Overall PI, PI for method failures and pregnancy ratio in females of all ages, and in females > 35 years **Exploratory:**[e] • PI for evaluable cycles in all females aged ≤ 35 years, and by BMI and weight subgroups based on confirmed, confirmed and suspected, and nonconfirmed pregnancies • Overall PI based on confirmed, confirmed and suspected, and nonconfirmed pregnancies in total and by BMI and weight subgroups **Safety and tolerability:** • Vaginal bleeding pattern • Study drug acceptability • Harms

Detail	Study 301	Study 302	Study 303
Publication status			
Publications	Archer (2015)[27] EudraCT Number: 2010 to 021787 to 15	Palacios (2019a)[28] Palacios (2019b)[29] EudraCT Number: 2011 to 002396 to 42	Kimble (2020)[30] ClinicalTrials.gov Number: NCT02269241

ASC-US = atypical squamous cells of undetermined significance; BMI = body mass index; DBP = diastolic blood pressure; IUD = intrauterine device; Pap = Papanicolaou; PI = Pearl Index; RCT = randomized controlled trial, SBP = systolic blood pressure.

Note: Six additional reports were included: FDA Multidisciplinary Review,[31] Health Canada reviewer report,[32] Archer et al. (2015),[27] Palacios et al. (2019a),[28] Palacios (2019b),[29] and Kimble et al. (2020).[30]

[a]This was also applicable for females who were not breastfeeding . Females who were breastfeeding could be included 6 weeks after delivery irrespective of menstrual cycles postdelivery.

[b]Study 301 prohibited medications that included injectable hormonal methods of contraception within the last 6 months, progestin-releasing IUDs or contraceptive implants within the last 2 months, and antiretroviral therapy within the last 6 months. Patients requiring long-term use of the following drugs were excluded from the study: anticonvulsants, barbiturates, rifampicin, atorvastatin, bosentan, griseofulvin, phenylbutazon, St. John's wort, or medications that may increase serum potassium (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and nonsteroidal anti-inflammatory drugs).

[c]Study 302 prohibited medications that included injectable hormonal methods of contraception within the last 6 months, progestin-releasing IUDs or contraceptive implants within the last 2 months, antiretroviral therapy within the last 6 months, microsomal enzyme–inducing drugs within the last 28 days before the start of study drug. Prohibited comedications included estrogens, progestogens, activated charcoal, microsomal enzyme–inducing drugs, anticonvulsants (e.g., hydantoins, phenytoin, carbamazepine, oxcarbazepine, topiramate, felbamate, and primidone), barbiturates, antibiotics (such as rifabutin or rifampicin), ritonavir, nelfinavir, atorvastatin, bosentan, griseofulvin, phenylbutazon, St. John's wort, or medications that may increase serum potassium.

[d]Study 303 prohibited medications that included injectable hormonal methods of contraception within the last 6 months (or depot medroxyprogesterone within the past 10 months), and progestin-releasing IUDs or contraceptive implants within the last 2 months. Patients requiring long-term use of the following drugs were excluded from the study: anticonvulsants, barbiturates, rifampicin, atorvastatin, bosentan, griseofulvin, phenylbutazon, or St. John's wort.

[e]All efficacy analyses in Study 303 were limited to nonbreastfeeding patients according to the study's protocol.

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] Clinical Study Report for Study 303,[16] and the sponsor's Summary of Clinical Evidence.

Interventions

In Study 301 and 303, all patients received an open-label study drug that consisted of drospirenone 4 mg white active tablets from day 1 to day 24, followed by inert green tablets from day 25 to day 28. The treatment duration was 13 cycles.

In Study 302, patients were randomly assigned to either drospirenone oral tablets using a 28-day regimen, with the administration of drospirenone 4 mg white active tablets from day 1 to day 24, followed by inert green tablets from day 25 to day 28 plus a placebo of desogestrel 0.075 once daily or a desogestrel 0.075 mg oral tablet administered once daily plus placebo of drospirenone using the same 28-day regimen as inert white or green tablets. The reference product and the reference placebo were identical in size, colour, and packaging. The treatment duration was 9 cycles.

In all 3 studies, patients were required to document all doses of the study drug taken, missed doses, any other contraceptives used, and sexual activity using an electronic diary. Patients also documented any vaginal bleeding or spotting, and bleeding intensity for each medication cycle. For all trials, if the time between ingestion of active tablets was more than 48 hours (i.e., subsequent dose was > 24 hours late), the patient was advised to use an additional method of contraception (barrier method) for the next 7 days. Additional contraception was recommended if vomiting occurred within 3 or 4 hours of ingesting a tablet.

Study participants agreed not to use other forms of contraception during the trials, with the exception of the occasional use of barrier methods to prevent infection, or as needed in the case of missed doses of

the study drug. In all studies, concomitant use of estrogens, progestogens, barrier contraceptive methods (except as described above), spermicides, emergency contraception, IUDs or other contraceptives, and activated charcoal within 3 hours of ingestion of a dose of study drug were prohibited.

The following previous therapies were not permitted in any of the studies: injectable hormonal contraceptives within the last 6 months (or 10 months for depot medroxyprogesterone acetate in Study 303 only); and progestin-releasing IUDs or contraceptive implants within the last 2 months. Study 301 and Study 302 prohibited the use of antiretroviral therapy within the last 6 months. In Study 302, microsomal enzyme–inducing drugs within the last 28 days, and in Study 303, use of medications containing human chorionic gonadotropin within the past month were prohibited. Patients requiring long-term use of the following drugs were excluded from the studies: anticonvulsants, barbiturates, antibiotics such as rifampicin, atorvastatin, bosentan, griseofulvin, phenylbutazon, and St. John's wort. In addition, patients were prohibited from taking medications that may increase serum potassium (Study 301 and Study 302) or microsomal enzyme–inducing drugs (Study 302).

Patients were withdrawn from the study or stopped the study drug if they became pregnant or if they wished to become pregnant, requested to be withdrawn, had a major protocol violation, adverse event, or other safety or ethical concerns.

Outcomes

A list of efficacy end points assessed in this Clinical Review is provided in Table 6, followed by descriptions of the outcome measures. Summarized end points are based on outcomes included in the sponsor's Summary of Clinical Evidence as well as any outcomes identified as important to this review according to the clinical expert consulted by CADTH and public drug plans. Stakeholder input from patient and clinician groups is also considered when selecting end points, but no inputs were received for this review. Using the same considerations, the CADTH review team selected end points that were considered to be most relevant to inform CADTH's expert committee deliberations and finalized this list of end points in consultation with members of the expert committee. All summarized efficacy end points were assessed using GRADE. Select notable harms outcomes considered important for informing CADTH's expert committee deliberations were also assessed using GRADE.

Table 6: Outcomes Summarized From the Studies Included in the Systematic Review

Outcome variable	Time point (cycles[a])	Study 301	Study 302	Study 303
Efficacy				
Corrected PI	Up to 9	NA	Secondary	NA
	Up to 13	Secondary	NA	NA
PI from evaluable cycles	Up to 13	NA	NA	Primary
Overall PI	Up to 9	NA	Primary	NA
	Up to 13	Primary	NA	Secondary

Outcome variable	Time point (cycles[a])	Study 301	Study 302	Study 303
Safety or tolerability				
Drug acceptability	Up to 13	Exploratory	NA	Secondary
Patients with unscheduled and scheduled vaginal bleeding or spotting	Up to 9	NA	Secondary[b]	NA
	Up to 13	Secondary	NA	Secondary
Discontinuation due to menstruation and uterine bleeding-related AEs	Up to 9	NA	Other	NA
	Up to 13	Other	NA	Other
AEs (hyperkalemia or VTE)	Up to 9	NA	Secondary	NA
	Up to 13	Secondary	NA	Secondary

AE = adverse event; PI = Pearl Index; NA = not applicable; VTE = venous thromboembolism.

[a]A medication cycle was defined as 28 days starting with the administration of the first tablet from the blister pack containing 28 tablets and ending with the last day of intake.

[b]Patients with scheduled bleeding were not reported in Study 302.

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] Clinical Study Report for Study 303,[16] and the sponsor's Summary of Clinical Evidence.

Based on input received, the corrected PI, the PI for evaluable cycles, and the overall PI were selected as the key efficacy outcomes. According to the expert consulted by CADTH, the PI is commonly used in clinical practice to help inform patients' decisions about contraception. The clinical expert also indicated that, because scheduled and unscheduled bleeding and/or spotting are important considerations for patients when selecting a contraceptive method, the number and percentage of patients with bleeding and/or spotting and withdrawals due to bleeding and/or spotting were included as key outcomes. Further, the clinical expert noted that measures of acceptability were important to patients. According to the expert consulted by CADTH for this review and FDA guidance, subgroup analyses for females aged 35 years and younger, and by BMI group, were identified as important. The clinical expert, CADTH Canadian Drug Expert Committee presenters, and the clinical trials' protocols identified hyperkalemia and VTE as adverse events of special interest. Based on input from the clinical expert, the GRADE assessment focused on the overall study populations (i.e., all age groups), as this population was deemed most generalizable to clinical practice and was consistent with the Health Canada indication.

The pregnancy ratio (life-table analysis) was not selected as a key efficacy measure by the clinical expert, but it was included in Appendix 1 because it is recommended by the FDA and European Medicines Agency as a supportive measure to the PI.[33,34] The method failure for the PI was not selected based on input from the clinical expert due to issues related to generalizability.

Pearl Index

In all trials, blood and/or urine pregnancy tests were conducted before the start of the study, after every cycle, and at the final follow-up visit of all trials. In Study 303, patients who reported a positive urine home pregnancy test had pregnancy confirmed by a qualitative urine pregnancy test (beta human chorionic gonadotropin) and a quantitative serum pregnancy test. Patients who reported a positive home urine test but

did not have pregnancy confirmed were labelled as suspected, nonconfirmed pregnancy. In Study 303, the date of conception was confirmed based on ultrasound and/or pelvic and abdominal examination.

The overall PI was the primary outcome of Study 301 and Study 302, and a secondary outcome of Study 303. It reports the number of pregnancies per 100 PYs of exposure. It was calculated by dividing the number of pregnancies by the total number of cycles of exposure and multiplying by 1,300 (to convert pregnancies per cycle to pregnancies per 100 PYs). Pregnancies following premature termination of the study drug were to be excluded from calculations unless intravaginal ultrasound examination and beta human chorionic gonadotropin testing were not performed to determine whether the date of conception was after the premature discontinuation.

In Study 301 and Study 302, the corrected PI was calculated based on the total number of cycles of exposure, excluding any medication cycles in which back-up contraception was used or no sexual activity occurred.

The primary efficacy variable in Study 303 was defined as the PI from evaluable cycles in females aged 35 years or younger (at the time of trial enrolment) who were not breastfeeding. The PI for evaluable cycles was calculated by dividing the sum of all on-drug pregnancies by the total number of evaluable cycles and multiplying by 1,300. An on-drug pregnancy included all conceptions that occurred from day 1 (the initiation of study medication) through 7 days after the final tablet (active or placebo) was taken. Evaluable cycles were defined as exposure cycles with intercourse without the use of back-up contraception at least once per cycle, based on the electronic diary question “Did you have sexual intercourse since the beginning of the cycle?” and answered with: “Yes I had sexual intercourse without additional contraception.” Also, a cycle was defined as evaluable if the patient became pregnant at the respective cycle regardless of whether back-up contraception was used, or the patient did not answer the question in the electronic diary about intercourse or answered, “I had no sexual intercourse at all,” but became pregnant at the respective cycle. A cycle was defined as nonevaluable if the patient did not become pregnant and had sexual intercourse with additional contraception, had no sexual intercourse at all, or the cycle had a missing diary answer about intercourse.

Acceptability

In Study 301, study drug acceptability was assessed from the patient’s and the investigator’s perspectives. At the end of cycle 1 and cycle 13 (or early discontinuation visit) patients were asked the following questions:

- How did you tolerate the intake of the study medication?
- How was your well-being during the intake of the study medication?

Answer options were excellent, good, moderate, or bad.

Patients who switched from another oral contraceptive to the study medication were asked to answer an additional question:

- How was your well-being during the intake of the study medication in comparison to the time when you took your former oral contraceptive?

Answer options were better, unchanged, or worse.

The investigator asked for a rating of the acceptability of the study drug from the physician's point of view. Answer options were excellent, good, moderate, or bad.

In Study 303, at the end of cycles 3 and 13 (or the early discontinuation visit), patients were asked by the investigator for an assessment of the acceptability of drospirenone, based on the following question:

- Are you satisfied with this method?

Answer options were strongly agree, agree, undecided, disagree, and strongly disagree.

Additionally, participants who switched from another oral contraceptive to the study drug were asked:

- How was your well-being during the intake of the study medication in comparison to the time when you took your former oral contraceptive?

Answer options were better, unchanged, worse, and no answer.

Harms

Adverse events were defined as any untoward medical occurrence in a patient who had received a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. TEAEs were defined as adverse events that started at or after the first administration of the study drug, events that started before the first administration of the study drug but which worsened after the first intake, and events starting after the last administration of the study drug but within the follow-up period.

Serious adverse events included any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization or prolonged hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or an important medical event that required intervention to prevent a serious adverse event. Any patient who became pregnant was followed until 3 months after parturition, and any abnormal outcome was reported as a serious adverse event.

In the protocol of the clinical trials, hyperkalemia and VTE (deep-vein thrombosis or pulmonary emboli) were identified as adverse events of special interest. Discontinuation due to menstruation or uterine bleeding was reported in Study 301 and Study 302, and the sponsor provided additional data for this outcome for Study 303. Patients included in this group were those who stopped treatment due to any of the following adverse events: amenorrhea, dysmenorrhea, dysfunctional uterine bleeding, menorrhagia, menstruation irregular, metrorrhagia, oligomenorrhea, uterine hemorrhage, and vaginal hemorrhage.

For all studies, the following end points related to bleeding pattern were defined:

- Bleeding: evidence of blood loss that requires the use of sanitary protection with a tampon, pad or pantyliner
- Spotting: evidence of minimal blood loss that does not require new use of any type of sanitary protection, including pantyliners

- 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
- 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.

Statistical Analysis

The key efficacy outcomes for all studies were reported descriptively as there was no comparator group in Study 301 and 303, and in Study 302 there was no planned statistical testing of contraceptive efficacy for drospirenone versus desogestrel. The PI was calculated as described in the outcomes section, with the 95% CI, constructed by inverting the limiting chi-square distribution under an assumed conditional Poisson distribution of the rate of pregnancy per cycle following a recommendation described in Gerlinger et al. (2003). With regard to the treatment acceptability questionnaire, the frequency of responses was reported based on available data for Study 301 and Study 303. There was no imputation for missing data for any outcome in the trials.

Study 302 also included a preplanned pooled analysis of efficacy end points for all patients in Study 301 and Study 302 (overall PI, corrected PI, PI for method failures and pregnancy ratio) for the overall study population as well as patients 35 years of age and younger.

In all 3 studies descriptive data were reported for the proportion of patients who discontinued the study drug due to menstrual or uterine bleeding–related TEAEs, hyperkalemia, and VTE events. The number of patients and rate of bleeding or spotting per cycle were reported descriptively for the combined reference periods (e.g., cycle 2 to 4, cycle 5 to 7, and so forth). All 3 studies reported data for unscheduled bleeding, but only Study 301 and Study 303 reported on scheduled bleeding. Study 302 included a planned analysis of the proportion of patients with unscheduled bleeding or spotting in cycle 2 to 6 for which a chi-square test was used to test the noninferiority of drospirenone versus desogestrel, assuming a 9% noninferiority margin. As desogestrel is not a comparator of interest in Canada, this analysis was not included in the CADTH report.

The cumulative probability of pregnancy (i.e., pregnancy ratio) was included in this report as a supplementary end point and was estimated using the Kaplan-Meier estimator. Patients who did not become pregnant were censored at the last intake of the study drug, and those who became pregnant were censored on the estimated date of conception.

The sample sizes in Study 301 and Study 302 were determined to meet the requirements of the Committee for Medical Products for Human Use *Guideline on Clinical Investigation of Steroid Contraceptives in Women*,[33] which states any new contraceptive should have been studied in at least 400 patients who completed 1 year of treatment. In addition, the number of cycles collected should be at least large enough to obtain the desired precision for the estimate of contraceptive efficacy, such that the difference between the 95% CI upper limit and the point estimate of the overall PI does not exceed 1.[33] The estimated total number of cycles required to meet the European Medicines Agency's precision requirements for 90% power was 12,337, if the true PI was less than 1.0. Study 301 and Study 302 were each estimated to provide half of the total evaluable cycles

needed for an assumed PI of less than 1 (with 90% power). With a possible dropout rate of 25%, 700 patients in Study 301 and 857 patients in Study 302 would need to be enrolled to have at least 6,169 cycles per study and 400 patients with 1 year of treatment.

In the initial protocol of Study 303, the study would need to enrol 675 patients aged 35 years or younger to have 4,500 evaluable cycles (after correction for use of back-up of contraception and sexual activity). The sample size was calculated assuming the PI was 3.0 or less (with an upper 95% CI that did not exceed 5.0). On average there would be 8.9 cycles per patient, and 24.8% of patients would use back-up contraception or engage in no sexual activity. In addition, 75 patients who were older than 35 years were planned for enrolment. Based on a protocol amendment after the start of the study (November 2015), the sample size was increased to 920 females aged 35 years or younger who were not breastfeeding at the start of the study, plus 75 females aged over 35 years. The goal was to obtain 5,000 evaluable cycles, assuming that 45% of patients would drop out prematurely. No citations were provided to support the assumptions used when calculating the sample size.

Subgroup analyses were planned for efficacy outcomes in females 35 years of age or younger in Study 301 and Study 302. Study 303 reported efficacy outcomes for females 35 years or younger, those aged over 35 years, and females of all ages. Study 303 also conducted subgroup analyses based on BMI (< 30 kg/m^2 or ≥ 30 kg/m^2), and weight (< median or ≥ median).

Table 7: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Handling of missing data	Subgroup analyses
Study 301 and Study 302				
Overall PI	2-sided 95% CIs (assuming a Poisson distribution)	NA	NA	Age group subgroup ≤ 35 years
PI after correction for additional contraception and sexually active cycles	2-sided 95% CIs (assuming a Poisson distribution)	NA	Missing data were not replaced	Age group subgroup ≤ 35 years
Cumulative pregnancy ratio[a]	Discreet interval Kaplan-Meier method, and Clopper-Pearson 95% CIs	NA	Missing data were not replaced	Age group subgroup ≤ 35 years
Acceptability (Study 301 only)	Descriptive data	NA	Based on patients with nonmissing data	NA
Study 303				
PI from evaluable cycles in females who were not breastfeeding and were aged: • ≤ 35 years	2-sided 95% CIs (assuming a Poisson distribution)	NA	Based on patients with nonmissing data in the MFAS[b]	Weight (< median or ≥ median) BMI (< 30 kg/m^2 or ≥ 30 kg/m^2)

End point	Statistical model	Adjustment factors	Handling of missing data	Subgroup analyses
• > 35 years • All ages				
Overall PI in females aged: • ≤ 35 years • > 35 years • All ages	2-sided 95% CIs (assuming a Poisson distribution)	NA	Based on patients with nonmissing data in the MFAS[b]	Weight (< median or ≥ median) BMI (< 30 kg/m^2 or ≥ 30 kg/m^2)
Cumulative pregnancy ratio[a] in females aged: • ≤ 35 years • > 35 years • All ages	Discreet interval Kaplan-Meier method	NA	Based on patients with nonmissing data in the MFAS[b]	NA
Acceptability	Descriptive data	NA	Based on patients with nonmissing data in the MFAS[b]	NA

CI = confidence interval; MFAS = modified full analysis set; NA = not applicable; PI = Pearl Index.

[a]The cumulative pregnancy ratio estimates the cumulative pregnancy probability and was included in this report as a supplementary outcome only.

[b]The MFAS population included only nonbreastfeeding patients.

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] Clinical Study Report for Study 303,[16] and the sponsor's Summary of Clinical Evidence.

Analysis Populations

The analysis populations for the efficacy, safety and tolerability outcomes are described in Table 8.

Study 303 included patients who were breastfeeding. However, these patients were excluded from the modified full analysis set (FAS) population, which was used for all efficacy analyses. Patients who were breastfeeding were excluded from enrolling in Study 301 and 302.

Table 8: Analysis Populations of Study 301, Study 302, and Study 303

Study	Population	Definition	Application
301	SS	All patients who had received at least 1 dose of study drug	All safety and tolerability analyses
	FAS	All patients who were included in the SS and who were not pregnant at the date of the first study drug intake	All efficacy analyses
302	SS	All patients who were randomized, had received at least 1 dose of study drug and had at least 1 postbaseline assessment of any safety or tolerability measurement	All safety analyses
	FAS	All patients who were included in the SS and had at least 1 postbaseline assessment of any efficacy measurement	All efficacy and tolerability analyses
303	SS	All patients who received at least 1 dose of study drug	All safety analyses
	FAS	All patients who received at least 1 study drug and who were not pregnant at the date of first study drug intake	All tolerability analyses

Study	Population	Definition	Application
	MFAS	All nonbreastfeeding patients who received at least 1 study drug and who were not pregnant at the date of first study drug intake	All efficacy analyses

FAS = full analysis set; MFAS = modified full analysis set; SS = safety set.

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] Clinical Study Report for Study 303,[16] and the sponsor's Summary of Clinical Evidence.

Results

Patient Disposition

The patient disposition for the 3 key studies is shown in Table 9. In Study 301, 824 patients were screened, of whom 724 (88%) were allocated to treatment, and 713 (87%) received drospirenone. The most common reasons for screening failure were ineligibility and withdrawal of consent. Over the 13-cycle trial, 198 patients (28%) discontinued early, most commonly due to adverse events (88 patients, or 12%), or withdrawal of consent (78 patients, or 11%).

Study 302 screened 1,365 patients, of whom 1,213 (89%) were randomized to drospirenone (872) or desogestrel (341). Fourteen patients (1.6%) in the drospirenone group withdrew before receiving treatment, leaving 858 patients who were treated. Over the 9-cycle treatment period, 170 patients (20%) discontinued early due to adverse events (82 patients, or 10%), withdrawal of consent (57 patients, or 7%), or other reasons (Table 9).

In Study 303, 1,552 patients were screened, and 546 (35%) were excluded, primarily due to ineligibility or withdrawal of consent. A total of 1,006 patients received drospirenone and 654 patients (65%) discontinued early from the 13-cycle trial. The most common reasons for withdrawal were lost to follow-up (269 patients, or 27%), withdrawal of consent (155 patients, or 15%), and adverse events (113 patients, or 11%). In study 303, most patients who prematurely discontinued, did so in the first 3 cycles (171 patients [17%] in cycle 1, 80 patients [8%] in cycle 2 and 89 patients [9%] in cycle 3).

The number of patients listed in Table 9 for Study 303 excludes 63 patients enrolled at 2 study sites (Site 104 and 120) who had serious breaches of FDA regulations, good clinical practices, or study protocol requirements. This included lack of patient oversight and data quality issues, and noncompliance with regulations and policies. The Institutional Review Board recommended that the data from these sites should be excluded because the accuracy of the data could not be confirmed. The sponsor closed the sites and excluded data from the analysis. Site 104 had enrolled 24 patients, of whom 2 completed the trial, 8 did not start treatment, and 14 discontinued prematurely (1 of whom became pregnant). In Site 120, a total of 30 patients were enrolled; 8 completed the study, 16 did not start treatment, and 15 discontinued prematurely (1 became pregnant).

Table 9: Summary of Patient Disposition From Studies Included in the Systematic Review

Patient disposition	Study 301	Study 302		Study 303[a]
	Drospirenone	Drospirenone	Desogestrel	Drospirenone
Screened, N	824	1,365		1,552[a]
Screening failures, N (%)	100 (12.1)	152 (11.1)		546 (35.2)
Reason for screening failure, N (%)				
Withdrawal of consent	24 (2.9)	55 (4.0)		73 (4.7)
Ineligibility	45 (5.5)	86 (6.3)		380 (24.5)
Adverse event	22 (2.7)	NA		NA
Other	9 (1.1)	11 (0.8)		31 (2.0)
Allocated to treatment, N	724	872	341	1,006
Treated, N	713	858	333	1,006
Not treated, N (%)	11 (1.5)	14 (1.6)	8 (2.3)	NA
Reason for not being treated, N (%)				
Withdrawal of consent	5 (0.7)	8 (0.9)	6 (1.8)	NA
Investigator's opinion	NA	1 (0.1)	NA	NA
Ineligibility	3 (0.4)	2 (0.2)	NA	NA
Pregnancy	1 (0.1)	2 (0.2)	NA	NA
Adverse event	NA	NA	1 (0.3)	NA
Lost to follow-up	NA	NA	NA	NA
Other	2 (0.2)	1 (0.1)	1 (0.3)	NA
Discontinued from study, N (%)	198 (27.8)	170 (19.8)	83 (24.9)	654 (65.0)
Reason for discontinuation, N (%)				
Withdrawal of consent	78 (10.9)	57 (6.6)	28 (8.4)	155 (15.4)
Investigator's opinion	1 (0.1)	NA	NA	7 (0.7)
Sponsor's request	NA	NA	NA	20 (2.0)
Major protocol violation or noncompliance	1 (0.1)	5 (0.6)	3 (0.9)	1 (0.1)
Pregnancy	2 (0.3)	4 (0.5)	1 (0.3)	15 (1.5)
Wish for pregnancy	2 (0.3)	4 (0.5)	1 (0.3)	5 (0.5)
Ineligibility	4 (0.6)	5 (0.6)	3 (0.9)	16 (1.6)
Adverse event	88 (12.3)	82 (9.6)	44 (13.2)	113 (11.2)
Lost to follow-up	NA	NA	NA	269 (26.7)
Other	22 (3.1)[c]	13 (1.5)	3 (0.9)	53 (5.3)
FAS, N (%)	713 (98.5)	858 (98.4)	332 (97.4)	1,004 (99.8)

Patient disposition	Study 301	Study 302		Study 303[a]
	Drospirenone	Drospirenone	Desogestrel	Drospirenone
Modified FAS, N (%)	NA	NA	NA	993 (98.7)[b]
Safety, N (%)	713 (98.5)	858 (98.4)	332 (97.4)	1,006 (100)

FAS = full analysis set; NA = not applicable.

[a]Two study sites (104 and 120) had serious regulation breaches and all data from the 63 patients enrolled at these sites were excluded from the analyses.

[b]The modified FAS included all females who were not breastfeeding.

[c]Other reasons included patients who were nonadherent and lost to follow-up, those who refused to complete electronic diaries, and patients who left the country.

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] Clinical Study Report for Study 303,[16] and the sponsor's Summary of Clinical Evidence.

Baseline Characteristics

The baseline characteristics outlined in Table 10 are limited to those that are most relevant to this review or were considered likely to affect the outcomes or interpretation of the study results.

The mean age of patients in the European Study 301 and Study 302 was 28.7 years (SD = 7.1) and 28.9 years (SD = 7.1), respectively, and 20% of patients were over 35 years of age in both studies. In both studies, the vast majority (> 99%) of patients were white, with a mean BMI of less than 30 kg/m^2 (94% to 97%). Most patients were nonsmokers (67% to 69%), while 26% to 28% of patients were current smokers, and 15% to 17% of patients had 1 or more VTE risk factors. Overall, the baseline characteristics were similar between Study 301 and Study 302.

Compared to the European studies, the US trial had fewer patients aged over 35 years, more racial diversity, higher mean weights and BMIs, more patients with VTE risk factors, and fewer current smokers but more former smokers. The mean age was 27.5 years (SD = 5.9), including 78 patients (8%) who were aged over 35 years. Although adolescents were eligible to enter the study, none were enrolled. The most common ethnicity or race reported was white (57%) followed by Black or African American (36%). More patients had a mean BMI of 30 kg/m^2 or less (65%) versus a BMI greater than 30 kg/m^2 (35%), and 39% had at least 1 VTE risk factor (most commonly due to obesity). The study included 67% of patients who were nonsmokers, 18% who were current smokers, and 15% who were former smokers.

The baseline characteristics of Study 303 were based on the total population (breastfeeding or not breastfeeding, N = 1,006); however, all efficacy results were calculated using the nonbreastfeeding population (N = 995). Eleven patients who were breastfeeding provided safety data only. The Clinical Study Report did not include all baseline characteristics of the nonbreastfeeding population, but, based on the information available, the demographics, mean weight, and blood pressure appeared to be similar to those of the overall study population. The Clinical Study Report also did not include the baseline characteristics for the subgroup of patients who were aged 35 years or younger. This younger subgroup was analyzed for the primary outcome of Study 303.

Table 10: Summary of Baseline Characteristics From Studies Included in the Systematic Review

Characteristic	Study 301 drospirenone (N = 713)	Study 302 drospirenone (N = 858)	Study 303 drospirenone (N = 1,006)
Age (years), mean (SD)	28.7 (7.1)	28.9 (7.1)	27.5 (5.9)
Age group, n (%)			
≤ 35 years	569 (79.8)	682 (79.5)	928 (92.2)
> 35 years	144 (20.2)	176 (20.5)	78 (7.8)
Ethnicity or race, n (%)			
Asian	1 (0.1)	0 (0)	20 (2.0)
American Indian or Alaska Native	0 (0)	0 (0)	13 (1.3)
Black or African American	1 (0.1)	2 (0.2)	358 (35.6)
Native Hawaiian or Pacific Islander	0 (0)	0 (0)	5 (0.5)
White	710 (99.6)	856 (99.8)	571 (56.8)
Other	1 (0.1)	0 (0)	39 (3.9)
Weight (kg), mean (SD)	63.5 (11.3)	63.4 (10.5)	76.7 (21.9)
BMI (kg/m^2), mean (SD)	23.0 (3.8)	23.0 (3.5)	28.6 (7.6)
BMI group, n (%)			
< 30 kg/m^2	672 (94.2)	828 (96.5)	652 (64.8)
≥ 30 kg/m^2	41 (5.8)	30 (3.5)	354 (35.2)
SBP (mm Hg), mean (SD)	NR	115.5 (10.4)	113.1 (11.1)
DBP (mm Hg), mean (SD)	NR	72.4 (8.0)	72.6 (8.6)
Blood pressure group, n (%)			
SBP < 130 mm Hg and DBP < 85 mm Hg	571 (80.1)	727 (84.7)	887 (88.2)
SBP ≥ 130 mm Hg and DBP ≥ 85 mm Hg	142 (19.9)	131 (15.3)	119 (11.8)
Venous thromboembolism risk factor, n (%)			
≥ 1 risk factor	110 (15.4)	142 (16.5)	394 (39.2)
Smoking status, n (%)			
Nonsmoker	493 (69.1)	575 (67.0)	675 (67.1)
Current smoker	182 (25.5)	237 (27.6)	182 (18.1)
Ex-smoker	38 (5.3)	46 (5.4)	147 (14.6)
Highest level of education, n (%)			
No high school diploma	6 (0.8)	15 (1.7)	36 (3.6)
Short-course or intermediate secondary school	183 (25.7)	188 (21.9)	NA

Characteristic	Study 301 drospirenone (N = 713)	Study 302 drospirenone (N = 858)	Study 303 drospirenone (N = 1,006)
High school diploma or equivalent	324 (45.4)	407 (47.4)	235 (23.4)
Some college	NA	NA	412 (41.0)
College or university degree	191 (26.8)	248 (28.9)	323 (32.1)
Other	9 (1.3)	NA	NA
Prior hormonal contraceptive use, n (%)			
Starter[a]	309 (43.3)	191 (22.3)	209 (20.8)
Direct switcher [b]	391 (54.8)	628 (73.2)	264 (26.2)
Indirect switcher[c]	NR	39 (4.5)	NR
Previous user without hormonal contraceptives for ≥ 3 months	NA	NA	463 (46.0)
Previous user without hormonal contraceptives for < 3 months	NA	NA	70 (7.0)
Unknown	13 (1.8)	0 (0)	NR

BMI = body mass index; DBP = diastolic blood pressure; NA = not applicable; NR = not reported; SBP = systolic blood pressure; SD = standard deviation.

[a]In Study 301, a starter is defined as: first administration of a hormonal contraceptive or had at least 1 day break after the administration of another hormonal contraceptive. In the Study 302 a starter is defined as: first administration of a hormonal contraceptive or at least a 4-month break between the administration of another hormonal contraceptive and study drug. In Study 303 a starter is defined as: first administration of a hormonal contraceptive.

[b]Direct switcher defined as: direct switch from another hormonal contraceptive to the study drug with no break in administration.

[c]Indirect switcher defined as: break between administration of another oral contraceptive and study drug is longer than 2 days and up to 4 months.

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] Clinical Study Report for Study 303,[16] and the sponsor's Summary of Clinical Evidence.

Exposure to Study Treatments

The mean exposure to drospirenone was 304.1 days (SD = 107.9) in Study 301, 222.7 days (SD = 65.8) in Study 302, and 197.3 days (SD = 144.4) in Study 303. The median adherence was 100% in all 3 studies (Table 11).

Table 11: Summary of Patient Exposure From Studies Included in the Systematic Review

Exposure	Study 301 drospirenone (N = 713)	Study 302 drospirenone (N = 858)	Study 303 drospirenone (N = 1,006)
Duration (days), mean (SD)	304.1 (107.9)	222.7 (65.8)	197.3 (144.4)
Duration (days), median (range)	364.0 (1 to 393)	252.0 (3 to 276)	168.0 (1 to 411)
Duration (days), interquartile range	280.0 to 364.0	252.0 to 252.0	NR
Cumulative exposure, n (%)			
≥ 28 days	NR	835 (97.3)	839 (83.4)
≥ 84 days	NR	787 (91.7)	674 (67.0)
≥ 168 days	NR	718 (83.7)	506 (50.3)
≥ 252 days	NR	673 (78.4)	420 (41.7)

Exposure	Study 301 drospirenone (N = 713)	Study 302 drospirenone (N = 858)	Study 303 drospirenone (N = 1,006)
Adherence, median % (range)[a]	100 (63 to 352)	100 (74 to 350)	100 (14 to 1,500)
Missing pill category, n (%)			
1 to 3 pills missing	102 (14.3)	49 (5.7)	NR[b]
4 or more pills missing	52 (7.3)	73 (8.5)	NR[b]

NR = not reported; SD = standard deviation.

[a]Based on a pill count of medications returned to the study centres.

[b]While the Clinical Study Report for Study 303 did not report the number of patients who missed 1 or more pills, the report stated that most patients (69%, n = 576) had 9 or more missing electronic diary entries related to intake of the study drug.

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] Clinical Study Report for Study 303,[16] and the sponsor's Summary of Clinical Evidence.

Efficacy

Pearl Index

In the 2 European studies (301 and 302) the primary end point was overall PI, and the corrected PI was a secondary outcome (the corrected PI is based on cycles during which sexual activity occurred without back-up contraception).

In Study 301, a total of 3 pregnancies occurred during the trial, all of which were considered method failures (i.e., the patient was adherent to drospirenone near the time of conception and the date of conception was during the treatment period, extended by a maximum of 2 days). All pregnancies were in females who were 35 years of age or younger. For the total study population, the corrected PI was 0.54 pregnancies per 100 PYs (95% CI, 0.11 to 1.59) and the overall PI was 0.51 (95% CI, 0.11 to 1.49) (Table 12). In the subgroup of patients who were aged 35 years or younger, the corrected and overall PIs were 0.71 (95% CI, 0.15 to 2.06) and 0.66 (95% CI, 0.14 to 1.93), respectively (Appendix 1, Table 19). No subgroup data were available by BMI or body weight.

In Study 302, a total of 5 pregnancies were reported in the drospirenone group. All pregnancies were in females aged 35 years or younger, and all were deemed method failures. In addition, 6 posttreatment pregnancies were reported, but these were not included in the calculation of the PI. Among all patients enrolled, 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) (Table 12). In the younger subgroup (aged ≤ 35 years) the corrected PI was 1.40 (95% CI, 0.45 to 3.27) and the overall PI was 1.24 (95% CI, 0.40 to 2.90) (Appendix 1, Table 19). No other subgroup data were reported.

In the preplanned pooled analysis of Study 301 and Study 302, based on the FAS (N = 1,571), a total of 8 pregnancies were reported over 14,329 exposure cycles. The pooled corrected PI was 0.79 (95% CI, 0.31 to 1.56) for all patients, and 1.02 (95% CI, 0.44 to 2.01) for those aged 35 years or younger (N = 1,251; 11,145 cycles). The pooled overall PIs were 0.73 (95% CI, 0.31 to 1.43) for all patients treated with drospirenone patients and 0.93 (95% CI, 0.40 to 1.84) for the younger subgroup.

The primary end point for Study 303 was the PI for evaluable cycles among females aged 35 years or younger who were not breastfeeding (N = 915; modified FAS population). For this subgroup, a total of 12

females had confirmed on-drug pregnancies (1.3%) over 5,337 evaluable cycles, with a PI of 2.9 (95% CI, 1.5 to 5.1). The overall PI in this subgroup was 2.7 (95% CI, 1.4 to 4.7) (Appendix 1, Table 19). For the total nonbreastfeeding study population (N = 993), the overall PI was 2.4 (95% CI, 1.2 to 4.2) and the PI for evaluable cycles was 2.6 (95% CI, 1.3 to 4.5) (Table 12).

Additional data were available for Study 303 from the FDA Multidisciplinary Review of drospirenone.[31] The FDA states that the applicant submitted primary results based on 12 pregnancies, but following an FDA request, added 2 pregnancies that occurred in the 2 study sites that were excluded from the study due to clinical trial protocol deviations. The FDA identified 3 other pregnancies, for a total of 17. The 3 additional pregnancies were categorized by the sponsor as suspected, nonconfirmed pregnancies. The 18th person who became pregnant was breastfeeding and was not included in the PI calculation because the study's protocol specified only nonlactating females would be analyzed for efficacy. The FDA performed a "worst-case" analysis, whereby any on-drug pregnancy that could not be ruled out was counted. Based on 17 pregnancies and 5,547 evaluable cycles from 953 patients (≤ 35 years), the PI calculated by the FDA was 4.0 (95% CI, 2.3 to 6.4).[31]

In Study 303, the overall PI and the PI for evaluable cycles were similar in the subgroups with BMIs of less than 30 kg/m^2 and 30 kg/m^2 or greater. Numerical differences were noted for the subgroups based on body weight, with patients whose weight was less than the study median reporting a lower PI compared with the subgroup with a body weight higher than the median (Appendix 1, Table 19). The subgroup estimates were reported descriptively, and no hypothesis was tested.

Table 12: Pearl Index Outcomes in All Females Who Were Not Breastfeeding

Outcomes	Study 301 (FAS population) drospirenone (N = 713)	Study 302 (FAS population) drospirenone (N = 858)	Study 303 (MFAS population[a]) drospirenone (N = 993)
Corrected PI			
Total, N	713	858	NA
Pregnancy, n (%)[b]	3 (0.4)	5 (0.6)	NA
Exposure cycles	7,191	5,977	NA
Corrected PI (95% CI)[c]	0.54 (0.11 to 1.59)	1.09 (0.35 to 2.54)	NA
PI from evaluable cycles			
Total, N	NA	NA	993[a]
Pregnancy, n (%[b])	NA	NA	12 (1.2)
Exposure cycles	NA	NA	6,004
PI from evaluable cycles (95% CI)[d]	NA	NA	2.6 (1.3 to 4.5)
Overall PI			
Total, N	713	858	993[a]

Outcomes	Study 301 (FAS population) drospirenone (N = 713)	Study 302 (FAS population) drospirenone (N = 858)	Study 303 (MFAS population[a]) drospirenone (N = 993)
Pregnancy, n (%[b])	3 (0.4)	5 (0.6)	12 (1.2)
Exposure cycles	7,638	6,691	6,566
Overall PI (95% CI)	0.51 (0.11 to 1.49)	0.97 (0.32 to 2.27)	2.4 (1.2 to 4.2)

CI = confidence interval; FAS = full analysis set; MFAS = modified full analysis set; NA = not applicable; PI = Pearl Index.

Note: The PI is the number of pregnancies per 100 PYs of exposure.

[a]Following the study's protocol, the efficacy analyses included only nonbreastfeeding patients (993 of 1,006 patients enrolled and treated).

[b]The denominator for the calculation of percentages is the total number of patients in the FAS or MFAS.

[c]Corrected PI = overall PI after correction for additional contraception and sexual activity status.

[d]PI for evaluable cycles excludes exposure time during which no sexual intercourse occurred or back-up contraception was used.

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] and Clinical Study Report for Study 303.[16]

Appendix 1, Table 20, includes data on the cumulative pregnancy ratio at cycles 6, 9, and 13 for all studies, which was provided as a supportive outcome to the PI. For Study 301 and 302 the pooled cumulative pregnancy ratio was 0.72% (95% CI, 0.17 to 1.27) at cycle 13 for the overall population and 0.93% (95% CI, 0.21 to 1.64) for those aged 35 years or younger. In Study 303, the cumulative pregnancy ratio was 2.00% (95% CI, 0.79 to 3.19) at cycle 13 for the total nonbreastfeeding population, and 2.24% (95% CI, 0.87 to 3.58) for females aged 35 years or younger.

Acceptability

The available data on the acceptability of drospirenone from Study 301 and 303 are shown in Table 13 and Table 14. Acceptability data were missing or not reported for 6% of patients in Study 301 and 38% of patients in Study 303 at the last study visit.

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

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

Table 13: Acceptability of Drospirenone — Study 301

Questions and responses at end-of-study visit	Drospirenone (safety set, N = 713)
How did you tolerate the intake of the study drug? n (%)	
Number of patients included in the analysis [a]	698
Excellent	319 (46)
Good	259 (37)
Moderate	48 (7)
Bad	47 (7)
Missing	25 (4)
How was your well-being during the intake of the study drug? n (%)	
Number of patients included in the analysis[a]	698
Excellent	306 (44)
Good	270 (39)
Moderate	52 (7)
Bad	45 (6)
Missing	25 (4)
How was your well-being during the intake of the study drug in comparison to the time when you took your former oral contraceptive? n (%)	
Number of patients included in the analysis[b]	389
Better	127 (33)
Unchanged	172 (44)
Worse	82 (21)
No answer	8 (2)
Acceptability of the study drug from the physician's point of view, n (%)	
Number of patients included in the analysis	698
Excellent	325 (47)
Good	252 (36)
Moderate	64 (9)
Bad	34 (5)
Missing	23 (3)

Note: Total number of patients calculated by CADTH based on the sum of responses.

[a]Percentages are based on the number of assessed patients.

[b]Percentages are based on the number of assessed patients who were not naive users.

Source: Clinical Study Report for Study 301.[14]

Table 14: Acceptability of Drospirenone — Study 303

Questions and responses at end-of-study visit	Drospirenone (full analysis set, N = 1,004)
Is the patient satisfied with the method? n (%)	
Number of patients included in the analysis[a]	631
Strongly agree	273 (43)
Agree	211 (33)
Undecided	53 (8)
Disagree	56 (9)
Strongly disagree	30 (5)
No answer	8 (1)
How was the patient's well-being during the intake of the study drug in comparison to the time when she took her former oral contraceptive? n (%)	
Number of patients included in the analysis[b]	511
Better	156 (31)
Unchanged	214 (42)
Worse	74 (14)
No answer	67 (13)

Note: Total number of patients calculated by CADTH based on the sum of responses·

[a]Percentages are based on the number of assessed patients.

[b]Percentages are based on the number of assessed patients who were not naive users.

Source: Clinical Study Report for Study 303.[16]

Harms

Table 15 provides harms data.

Adverse Events

Treatment-emergent adverse events were reported by 348 patients (49%), 332 patients (39%), and 614 patients (61%) in Study 301, Study 302, and Study 303, respectively. Across the trials, the most common events were headaches (reported by 4% to 6% of patients), 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%).

Serious Adverse Events

Serious TEAEs were reported by 1.4% to 1.7% of patients enrolled in the trials. Serious hyperkalemia events were experienced by 4 patients (0.4%) in Study 303 and 1 patient (0.1%) in Study 302. Other events reported in 2 or more patients per treatment group were appendicitis, breast prosthesis implantation, cervical dysplasia, and fibroadenoma of the breast (Table 15).

Table 15: Summary of Harms Results From Studies Included in the Systematic Review

Adverse events	Study 301 (SS) drospirenone (N = 713)	Study 302 (SS) drospirenone (N = 858)	Study 303 (SS) drospirenone (N = 1,006)
Most common TEAE (frequency ≥ 3% in any treatment group), n (%)			
≥ 1 TEAE[a]	348 (48.8)	332 (38.7)	614 (61.0)
Acne	45 (6.3)	27 (3.1)	35 (3.5)
Breast pain	8 (1.1)	14 (1.6)	51 (5.1)
Breast tenderness	1 (0.1)	NR	33 (3.3)
Cervical dysplasia	14 (2.0)	26 (3.0)	29 (2.9)
Dysmenorrhea	2 (0.3)	8 (0.9)	58 (5.8)
Headache	32 (4.5)	38 (4.4)	64 (6.4)
Metrorrhagia	19 (2.7)	3 (0.3)	53 (5.3)
Nasopharyngitis	22 (3.1)	29 (3.4)	77 (7.7)
Nausea	10 (1.4)	3 (0.3)	63 (6.3)
Upper respiratory tract infection	1 (0.1)	5 (0.6)	36 (3.6)
Urinary tract Infection	6 (0.8)	5 (0.6)	34 (3.4)
Vaginal hemorrhage	10 (1.4)	32 (3.7)	12 (1.2)
Increased weight	12 (1.7)	21 (2.4)	34 (3.4)
Most common TESAE (reported in 2 or more patients in any treatment group), n (%)			
Patients with ≥ 1 TESAE	10 (1.4)	15 (1.7)	15 (1.5)
Appendicitis	NR	3 (0.3)	1 (0.1)
Breast prosthesis implantation	2 (0.3)	NR	NR
Cervical dysplasia	NR	2 (0.2)	NR
Fibroadenoma of breast	NR	2 (0.2)	NR
Hyperkalemia	NR	1 (0.1)	4 (0.4)
Most common reasons for stopping treatment due to TEAE (frequency ≥ 1% in any treatment group), n (%)			
Patients with ≥ 1 TEAE leading to discontinuation	88 (12.3)	82 (9.6)	113 (11.2)
Acne	21 (2.9)	9 (1.0)	8 (0.8)
Metrorrhagia	12 (1.7)	0	19 (1.9)
Menstruation irregular	9 (1.3)	NR	3 (0.3)
Vaginal hemorrhage	5 (0.7)	22 (2.6)	3 (0.3)
Increased weight	2 (0.3)	8 (0.9)	12 (1.2)
Deaths due to TEAEs			
Patients who died	0	0	0

Adverse events	Study 301 (SS) drospirenone (N = 713)	Study 302 (SS) drospirenone (N = 858)	Study 303 (SS) drospirenone (N = 1,006)
TEAEs of special interest			
Venous thromboembolism[a]	0	0	0
Hyperkalemia	0	1 (0.1)	5 (0.5)
Bleeding-related TEAE	57 (8.0)	46 (5.4)	NR
Discontinuation due to bleeding-related TEAEs[b]	30 (4.2)	28 (3.3)	39 (3.9)
Ovarian cyst	6 (0.8)	8 (0.9)	11 (1.1)
Ectopic pregnancy	NR	0	1 (0.1)

NR = not reported; SS = safety set; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

[a]Includes deep-vein thrombosis or pulmonary embolus.

[b]Includes amenorrhea, dysmenorrhea, dysfunctional uterine bleeding, menorrhagia, menstruation irregular, metrorrhagia, oligomenorrhea, uterine hemorrhage, and vaginal hemorrhage.

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] and Clinical Study Report for Study 303.[16] Additional data supplied by sponsor, October 11, 2023.[17]

Withdrawals Due to Adverse Events

Across the studies, 10% to 12% of patients discontinued due to adverse events, with bleeding-related events (3.3% to 4.2%), acne (0.8% to 2.9%), and increased weight (0.3% to 1.2%) being the most common reasons reported.

Mortality

No patients died during the studies.

Notable Harms

In the studies' protocols, VTE and hyperkalemia were identified as adverse events of special interest. No VTE adverse events 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 reported hyperkalemia. One patient experienced an ectopic pregnancy in Study 303 (0.1%), and 6 patients (0.8%), 8 patients (0.9%), and 11 patients (1.1%) had a TEAE due to an ovarian cyst in Study 301, Study 302, and Study 303, respectively.

Bleeding or Spotting

Bleeding-related TEAEs were reported by 57 patients (8%) in Study 301 and 46 patients (5%) in Study 302. (No relevant data were available for Study 303.) The proportion of patients who discontinued due to menstruation or uterine bleeding–related TEAEs ranged from 3.3% to 4.2% (Table 15).

The proportion of patients with scheduled or unscheduled bleeding or spotting was highest in cycle 2 to 4, and generally decreased over time (Table 16). In cycle 2 to 4, between 56% and 68% of patients reported scheduled bleeding, and 68% to 76% experienced unscheduled bleeding. In the last follow-up period (cycle 7 to 9 in Study 302 and cycle 11 to 13 in Study 301 and Study 303), 38% to 44% of patients reported scheduled bleeding or spotting, and 52% to 65% of patients reported unscheduled bleeding or spotting.

Table 16: Patients With Scheduled or Unscheduled Bleeding or Spotting

Cycle	Study 301 (SS, N = 713)			Study 302 (FAS, N = 858)			Study 303 (FAS, N = 1,004)		
	N	Scheduled	Unscheduled	N	Scheduled	Unscheduled	N	Scheduled	Unscheduled
Number of patients with bleeding or spotting, n (%)									
Cycle 2 to 4	634	428 (68)	480 (76)	527	NR	358 (68)	609	338 (56)	422 (69)
Cycle 5 to 7	569	316 (56)	408 (72)	423	NR	269 (64)	448	187 (42)	284 (63)
Cycle 8 to 10	536	276 (52)	367 (69)	374[a]	NR	243 (65)[a]	376	157 (42)	218 (58)
Cycle 11 to 13	499	221 (44)	320 (64)	NA	NA	NA	310	118 (38)	162 (52)

FAS = full analysis set; NA = not applicable; NR = not reported; SS = safety set.

[a]Cycle 7 to 9.

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] and Clinical Study Report for Study 303.[16]

Critical Appraisal

Internal Validity

Pivotal and Randomized Controlled Trials Included in the Systematic Review

Of the 3 trials that met the systematic review criteria, 2 were single-arm, open-label, nonrandomized trials (Study 301 and Study 303), and 1 was a double-blind RCT (Study 302). The RCT compared drospirenone with desogestrel, which is not approved in Canada and therefore is not a relevant comparator. Moreover, the RCT was not designed to assess the comparative contraceptive efficacy and no statistical testing was conducted between drospirenone and desogestrel for any efficacy end point. As such, the available efficacy and safety data for drospirenone are based on noncomparative evidence only. Guidance from regulators on the assessment of clinical effectiveness and safety for hormonal contraceptives notes that because a placebo group is not feasible (trial participants do not desire pregnancy and contraceptives typically have a sizable treatment effect), single-arm, open-label trials are generally adequate to establish efficacy and safety, as long as the trials are well conducted.[35] While the CADTH reviewer acknowledged that regulators do not require controlled trials for new hormonal contraceptive drugs for licensure,[33,34] comparative evidence is the focus of reimbursement reviews.

Aside from the study design, the key limitation of the trials was the extent of withdrawals. In the European studies (Study 301 and Study 302), 28% and 20% of patients, respectively, discontinued prematurely, but in the US study (Study 303), 65% of patients withdrew early. Across all 3 studies the proportion of patients who discontinued due to adverse events, withdrawal of consent, or other reasons were generally similar, except for lost to follow-up, which was reported for 27% of patients in Study 303 and few patients in the other 2 trials. In Study 303, the extent of early withdrawals was higher than expected, as the study sample-size estimates were based on an anticipated withdrawal rate of 45%. The potential impact of the early withdrawals on the findings of Study 303 is not clear. The FDA noted that the withdrawal rate in Study 303 was higher than that of some recent contraceptive trials in the US and Canada, but because this is the first large-scale study of a POP in many years, there is no contemporary comparator.[31] According to the clinical expert consulted by CADTH, because patients often switch between contraceptive methods, the

discontinuation rate for contraceptives in clinical practice may be high. The PI is based on exposure cycles and accounts for the follow-up time for each patient. While the extent of losses may not be a major source of bias for the estimates of the PI, it should be considered when interpreting acceptability and bleeding-related end points for all 3 studies. At the last follow-up time point, acceptability data were missing for 6% and 38% of patients in Study 301 and 303, and scheduled and unscheduled bleeding data were missing for 30%, 56%, and 69% of patients in Study 301, 302, and 303, respectively. There was no imputation for missing data, and all data reported were from patients who opted to continue treatment. Those remaining in the study may not be representative of the larger population, particularly for later time points, at which the number of patients reporting data may be low.

Two of the studies were open-label, but the lack of blinding was not considered a potential source of bias for the detection of pregnancy. However, the patients' expectations of treatment may influence reporting of subjective measures, such as acceptability or adverse events. The direction and magnitude of this potential bias remains unclear.

The methods used to calculate the PI appear to be consistent with those specified in regulatory guidance.[33,34] In Study 303, some on-treatment pregnancies were excluded from the primary analyses. The study reported 13 confirmed on-treatment pregnancies, 1 of which was in a patient who was breastfeeding and therefore excluded following the study's protocol. Another 5 confirmed or suspected pregnancies were also excluded from the analyses, including 2 that occurred in the 2 study sites that were closed due to serious breaches of FDA regulations and good clinical practice requirements. Inclusion of these additional pregnancies increased the PI for evaluable cycles to 4.0 (95% CI, 2.3 to 6.4) for the younger subgroup (aged ≤ 35 years).

The sponsor did not provide any evidence to support the validity and reliability of the questions used to measure treatment acceptability. In addition, there were issues with missing data, as only 62% of patients in Study 303 and 94% in Study 301 provided a response to the acceptability questions at their last study visit.

Descriptive data were reported on the number and proportion of patients with scheduled and unscheduled bleeding or spotting, and patients who stopped treatment due to bleeding or spotting. Data on bleeding-related outcomes were based on entries in electronic diaries, in which patients were asked to report on any bleeding they experienced. The CADTH reviewer was unable to find information on patients' adherence to diary entry protocols.

In all 3 studies, hyperkalemia and VTE were identified as safety outcomes of special interest, and data were specifically collected for these events which could improve the likelihood of detecting these uncommon adverse events.

External Validity

Overall, the clinical expert consulted for this review did not identify any major generalizability issues with the finding of the key clinical trials, although there were some differences with regard to distribution according to age, BMI, race, and concurrent conditions of the patients enrolled relative to Canadian clinical practice. All study participants were adults, with most patients (80% to 92%) aged less than 35 years. No adolescents were included in these trials, but the clinical expert stated that efficacy findings in adults would be

generalizable to younger persons. Only Study 303 allowed patients who were breastfeeding to enrol; however, breastfeeding patients (N = 11) were excluded from the efficacy analyses. All the studies excluded patients with a higher risk of VTE or those with specific comorbidities, such as cardiovascular, renal, or liver disease; diabetes with vascular involvement; and psychiatric or substance-use disorders. Due to these exclusions, the safety and efficacy of drospirenone in patients with these conditions is unclear.

There was limited information available on the 11% to 35% of patients who were screened but were not randomized. Because the characteristics of these patients were not reported, an assessment of heterogeneity was not conducted. None of the trials included Canadian patients, and the study populations may not reflect the racial distribution of Canada. In particular, the European studies had low racial diversity (> 99% white). In the US study, 57% of patients identified as white, 36% identified as Black or African American, and people of other races made up a small percentage of the trial. The European studies enrolled a lower percentage of patients with a BMI of 30 kg/m^2 or greater (4% and 6%) than would be expected in Canada. The US study included 35% of patients who had a high BMI. The studies showed some variation in contraceptive efficacy according to region, with the European studies reporting a lower pregnancy rate than the US study. Some of the variation in efficacy may be related to differences in the patient populations, and this should be considered when extrapolating the findings to the Canadian context.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the 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:[12,13]

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate — The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. We use the word "likely" for evidence of moderate certainty (e.g., "X intervention likely results in Y outcome").
- **Low certainty**: Our confidence in the effect estimate is limited — The true effect may be substantially different from the estimate of the effect. We use the word "may" for evidence of low certainty (e.g., "X intervention may result in Y outcome").
- **Very low certainty**: We have very little confidence in the effect estimate — The true effect is likely to be substantially different from the estimate of effect. We describe evidence of very low certainty as "very uncertain."

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, 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 very low certainty with no opportunity for rating up.

For the GRADE assessments, findings from Study 301, Study 302, and Study 303 were considered together and summarized narratively by 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 the PI for evaluable cycles appear to measure the same concept (PI corrected for sexual activity without back-up contraception), it was not clear that these end points were estimated using identical methods; the corrected PIs in Study 301 and Study 302 were therefore assessed separately from the PI for evaluable cycles in Study 303.

Results of GRADE Assessments

Drospirenone Versus Norethindrone

Table 2 presents the GRADE summary of findings for drospirenone versus norethindrone.

Long-Term Extension Studies

Study 304 included safety and tolerability findings among an adolescent population aged 12 to 17 years and was summarized in the section addressing gaps in the systematic review evidence.

Indirect Evidence

No indirect evidence was submitted by the sponsor. The sponsor stated that it was not feasible to conduct an indirect treatment comparison with norethindrone, the POP available in Canada. First, the sponsor concluded there would be too much heterogeneity for valid effect estimates between norethindrone and drospirenone, due to the significant differences in the time frame during which the norethindrone and drospirenone trials were conducted. All the norethindrone trials were conducted in the 1970s versus 2011 to 2014 for the drospirenone studies, and there would be substantial differences in trial design, study populations, and data collection and analysis methods between the treatments. Second, the sponsor stated that it would not be possible to form a connected network. Drospirenone has only been studied in comparison with desogestrel, and the sponsor was unable to find any trials comparing norethindrone and desogestrel.

Studies Addressing Gaps in the Systematic Review Evidence

The contents within this section were informed by materials submitted by the sponsor. The following summary was validated by the CADTH review team.

Description of Studies

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, i.e., female adolescents aged 12 to 17 years, which was a patient group not included in Study 301, Study 302, or Study 303. However, 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.

Study 304 was a multicentre, open-label, prospective, nonrandomized phase III trial of drospirenone 4 mg. The duration of the study was 6 cycles plus an optional 7-cycle extension.

Table 17: Details of Study Addressing Gaps in the Systematic Review Evidence

Detail	Study 304
Study design	Nonrandomized, multicentre, open-label, prospective, phase III trial
Enrolled, N	103 female adolescents
Key inclusion criteria	Female adolescents aged 12 to 17 years, with or without an intact hymen. • Postmonarcheal for at least 6 months • For starters: at least 4 menstrual cycles during the last 56 months were regular • Menstruation restarted since last pregnancy (only applicable for patients who were pregnant within the last 6 months) • SBP < 140 mm Hg, DBP < 90 mm Hg • Laboratory values with no deviations
Key exclusion criteria	• BMI below the fifth percentile or above the 95th percentile (adolescents' BMI-for-age percentiles) • Breastfeeding, pregnancy • Uncontrolled concomitant disease • Abnormal gynecological examination that contraindicates participation in the trial • Unexplained amenorrhea, polycystic ovary syndrome • Known contraindication or hypersensitivity to study drug, renal insufficiency, hepatic dysfunction, adrenal insufficiency, thrombophlebitis, thromboembolism, cerebrovascular or coronary-artery disease, valvular heart disease with thrombogenic complications, severe hypertension, diabetes mellitus with vascular involvement, headaches with focal neurologic symptoms, major surgery with prolonged immobilization, carcinoma of the breast or endometrium or other estrogen-dependent neoplasia, abnormal genital bleeding, cholestatic jaundice of pregnancy or jaundice with prior pill use, liver tumour and/or disease, or uncontrolled thyroid disorder • Alcohol, medication, or drug abuse (within the last 12 months) • Known bleeding disorder or history of unexplained bleeding or bruising within the last 12 months • Prohibited previous medication and/or contraceptive[a] • Regular administration of prohibited comedication[b] • Planned surgery during the anticipated time of participation in this trial requiring withdrawal of an oral contraceptive • Evidence or history of neurotic personality, psychiatric illness, or suicide risk
Intervention	Drospirenone oral tablet using a 24-plus-4–day regimen: • Day 1 to 24: drospirenone 4 mg white active tablets • Day 25 to 28: inert green tablets
Comparator(s)	None
Primary end point	• Vaginal bleeding pattern • Withdrawal due to TEAEs based on abnormal bleeding
Secondary end points	**Secondary:** • Vaginal bleeding pattern • Adverse events

Detail	Study 304
	• Clinical laboratory parameters • Vital signs • Gynecological examination findings • Intravaginal ultrasonography results • Physical examination findings. **Tolerability:** • Study drug acceptability
Publications	Apter (2020)[35]

BMI = body mass index; DPB = diastolic blood pressure; SBP = systolic blood pressure; TEAE = treatment-emergent adverse event.

[a]Prohibited previous medication and/or contraceptive: injectable hormonal methods of contraception within the last 6 months, progestin-releasing IUD or contraceptive implant within the last 1 months or antiretroviral therapy within the last 6 months.

[b]Prohibited comedication: estrogens, progestogens, activated charcoal, anticonvulsants (e.g., phenytoin, carbamazepine, oxcarbazepine, topiramate, felbamate, primidone), barbiturates, rifampicin, atorvastatin, bosentan, griseofulvin, phenylbutazon, St. John's wort (*Hypericum perforatum*), medications that may increase serum potassium (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and nonsteroidal anti-inflammatory drugs).

Source: Clinical Study Report for Study 304[36] and the sponsor's Summary of Clinical Evidence.

Populations

This study included female adolescents aged 12 to 17 years. A total of 103 adolescents were enrolled and allocated to treatment at 9 centres in Germany, Finland, Sweden, and Ukraine.

Interventions

All patients who were included in the study following the screening period received drospirenone oral tablets using a 28-day regimen:

- Day 1 to 24: drospirenone 4 mg white active tablets
- Day 25 to 28: green inert tablets

In the core phase of this trial, patients repeated this 28-day regimen for 6 treatment cycles or until specific withdrawal criteria were met. Following the core phase of the study, patients could continue treatment in an optional extension phase lasting 7 cycles.

Outcomes

The vaginal bleeding pattern (recorded using patient diaries) over the 6 cycles of the core phase was a primary end point of Study 304. The other primary outcome was withdrawals due to abnormal bleeding during the core phase of the trial.

Secondary end points included assessment of safety and tolerability. Table 18 provides detailed secondary outcomes.

Statistical Analysis

The analysis populations for Study 304 included the safety set, consisting of all patients who received at least 1 dose of the study drug; the core per-protocol set (CPPS), comprising all patients included in the safety set who did not present any major protocol deviations during the core phase; and the per-protocol set

(PPS), consisting of all patients who were included in the safety set and did not present any major protocol deviations during the trial.

The vaginal bleeding pattern data were analyzed on the safety set and the CPPS by means of summary statistics. Secondary safety and tolerability variables were analyzed for the safety set. The vaginal bleeding pattern data over 13 cycles were also analyzed for the PPS. Study drug acceptability data were analyzed for the safety set. Cycles without consecutively missing diary entries and with fewer than 5 nonconsecutive missing diary entries were to be used for the safety set and CPPS bleeding pattern analysis.

The sample-size calculation was not based on statistical considerations. Screening of about 130 patients was planned to have approximately 100 patients in the safety set.

Results

Patient Disposition

Patient disposition is summarized in Table 18. A total of 111 adolescents were enrolled; 8 patients had screening failures and 1 patient refused treatment, leaving 102 patients to receive drospirenone. Thirteen patients (12.7%) prematurely terminated the trial during the core phase, mostly due to adverse events. In total, 89 patients completed the core phase. Of these, 85 patients entered the extension phase, 11 (12.9%) prematurely terminated the extension phase, and 74 completed the extension phase. Primary reasons for premature trial termination during the extension phase were nonserious adverse events in 3.5%, withdrawal of consent in 2.4%, lost to follow-up in 2.4%, noncompliance in 1.2%, moved abroad in 1.2%, and study drug gap in 1.2%.

A total of 103 patients were allocated to treatment with drospirenone 4 mg. Of these, 102 patients received at least 1 dose of the study drug and were included in the safety set. Nine additional patients were excluded from the CPPS due to major protocol deviations during the core phase, leaving the CPPS with 93 patients. For the PPS, 15 patients with major protocol deviations (due to major protocol deviations during the trial) were excluded and 87 patients were analyzed.

Table 18: Patient Disposition — Study 304

Patient disposition	Drospirenone
Screened, N	111
Screening failures, N (%)	8 (7.2)
Reason for screening failure, N (%)	
Ineligibility	6 (5.4)
Lost to follow-up	1 (0.9)
Adverse event	1 (0.9)
Allocated to treatment, N	103
Treated, N	102[a]
Discontinued from study during core phase, N (%)	13 (12.7)

Patient disposition	Drospirenone
Reason for discontinuation, N (%)	
Withdrawal of consent	2 (2.0)
Noncompliance	1 (1.0)
Adverse event	9 (8.8)
Lost to follow-up	1 (1.0)
Completed core phase	89
Entered extension phase	85
Discontinued from study during extension phase, N (%)	11 (12.9)
Reason for discontinuation, N (%)	
Withdrawal of consent	2 (2.4)
Major protocol violation	1 (1.2)
Noncompliance	1 (1.2)
Adverse event	3 (3.5)
Lost to follow-up	2 (2.4)
Moved abroad	1 (1.2)
Study drug gap	1 (1.2)
Completed extension phase	74
CPPS, N	93
PPS, N	87
Safety set, N	102

CPPS = core per-protocol set; PPS = per-protocol set.

[a]One patient withdrew consent and did not receive study drug.

Sources: Clinical Study Report for Study 304[36] and the sponsor's Summary of Clinical Evidence.

Baseline Characteristics

All patients were adolescents aged between 12 and 17 years, with a mean age of 16.1 years (SD = 0.9). The majority of patients were graduates of high school (48.0%) or intermediate secondary school (32.4%). The vast majority (97.1%) of patients were white. The patients' mean weight at screening was 59.7 kg (SD = 8.37) and the mean BMI was 21.47 kg/m^2 (SD = 2.661). At screening, all patients were reported to have an SBP < 140 mm Hg, and DBP < 90 mm Hg. The patients' mean SBP was mm Hg 109.8 (SD = 9.4) and the mean DBP was 66.6 mm Hg (SD = 7.7). The vast majority of adolescents were nonsmokers (86.3%) and alcohol abstainers (75.5%). Finally, the majority (98.0%) of patients were assessed by the investigators as having no VTE risk factors, while 2.0% were reported to have a single VTE risk factor.

Patient Exposure

For the core and extension phase of Study 304, the mean number of days exposed to the investigational product was 312.3 (SD = 99.7) with a median duration of 364 days. A cumulative exposure of at least 84

days was achieved by 94.1% of patients, whereas a cumulative exposure of at least 252 days was achieved by 79.4% of patients. Concomitant medications were used by 71.6% of patients in Study 304.

Efficacy

Contraceptive efficacy outcomes have not been evaluated.

Data on the acceptability of drospirenone was collected for the 13 cycles and summarized based on the last nonmissing postbaseline study visit. A total of 100 patients provided responses to the acceptability questions. The majority of patients rated tolerability as "excellent" (47.1%), "good" (35.3%), or "moderate" (15.7%). None of the patients rated tolerability as "bad" at any scheduled time point. With regard to bleeding pattern, the majority of patients reported that 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%), the duration of vaginal bleeding (greatly improved: 25.5%; improved: 44.1%; not changed: 19.6%; worsened: 6.9%), and the 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

The vaginal bleeding pattern data were analyzed on the safety set, and on the CPPS (core phase) and PPS (core and extension phase). No noticeable differences were observed between the safety set and the CPPS, or between the safety set and PPS results. Of the 102 patients who received drospirenone in Study 304, a total of 89 provided bleeding-related data for cycle 2 to cycle 4 and 67 patients reported for cycle 11 to cycle 13.

During the 13-cycle study, a trend toward less bleeding was observed over time. Analyzed by 3-cycle reference periods, the proportion of patients who started bleeding or spotting on cycle day 25 to 28 ± 1 decreased from 65.2% during cycle 2 to cycle 4 to 38.8% during cycle 11 to cycle13. The proportion of patients with scheduled bleeding and/or spotting decreased from 77.5% during cycle 2 to cycle 4 to 43.3% during cycle 11 to cycle 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 (minimum to maximum = 0 to 68) in cycle 2 to cycle 4 to 11.0 days (minimum to maximum = 0 to 46) in cycle 11 to cycle 13. The median number of scheduled bleeding and/or spotting days decreased from 4.0 days (minimum to maximum = 0 to 18) in cycle 2 to cycle 4 to 0.0 days (minimum to maximum = 0 to 21) in cycle 11 to cycle 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 (minimum to maximum = 0 to 39) during cycle 11 to cycle 13.

The number of patients reporting absence of bleeding or spotting increased with continuous treatment, from 12 patients (13.5%) in cycle 2 to cycle 4 to 17 patients (25.4%) in cycle 11 to cycle 13.

The number of patients reporting dysmenorrhea decreased from 47 before screening to 14 at the end of cycle 6, and to 8 at the end of cycle 13.

During the core phase, 4 patients (4%) terminated the study due to abnormal bleeding (metrorrhagia). For the overall study period (core and extension phase) a total of 6 patients (6%) stopped treatment due to abnormal bleeding, including 5 patients due to metrorrhagia and 1 patient due to amenorrhea.

For the overall (core and extension) study period, 63.7% of patients experienced at least 1 TEAE. The most frequently reported TEAEs were nasopharyngitis (reported by 12.7%), acne (6.9%), viral respiratory tract infection (6.9%), headache (5.9%), abdominal pain (5.9%), bronchitis (5.9%) and viral infection (5.9%). The percentage of patients who experienced a serious TEAE was 2%. Only 2 patients reported serious TEAEs during the trial, these were joint dislocation (1.0%) and pharyngitis (1.0%). The percentage of patients who prematurely discontinued the trial due to TEAEs was 10.8%. The most frequently reported reason for discontinuation due to TEAEs was metrorrhagia (4.9%), and all other events (acne, amenorrhea, depression, mood alteration, mood swings and nausea) were each reported for 1 patient only.

Critical Appraisal

Internal Validity

Because this study was an open-label and nonrandomized trial, the lack of comparison with an active comparator precludes the ability to assess the relative therapeutic benefits or safety of drospirenone. The lack of blinding may affect patients' expectations of treatment and influence reporting of subjective measures such as acceptability or adverse events. The direction and magnitude of this potential bias remains unclear.

External Validity

There is a limitation regarding the generalizability of the results to the Canadian population, as the study populations are from Germany, Finland, Sweden, and Ukraine only.

Patients with specific comorbidities, psychiatric illness, specific BMIs, and alcohol or drug abuse were excluded from study. Due to these exclusions, the generalizability of the results to the individuals with those conditions is unclear.

Discussion

Summary of Available Evidence

The systematic review included 3 studies that provided evidence on the efficacy, safety, and tolerability of drospirenone in healthy adult females. Studies 301 and 303 were open-label, noncomparative, phase III trials, in which all patients received drospirenone for 13 cycles of 28 days. Each cycle consisted of 24 days of drospirenone 4 mg oral tablets, followed by inert tables for 4 days. Study 302 was a double-blind RCT that randomized patients to drospirenone 4 mg for nine 28-day cycles or desogestrel 0.075 mg daily. The primary and secondary outcomes of interest to this review were the overall PI, the corrected PI, and the PI for evaluable cycles.

Two trials were conducted in Europe (Study 301 and Study 302) and 1 (Study 303) was conducted in the US. Totals of 713, 858, and 1,006 patients received drospirenone for medians of 364, 252, and 168 days in Study 301, Study 302, and Study 303, respectively. The mean age of patients enrolled ranged from 27.5 years (SD = 5.9) to 28.9 years (SD = 7.1). In the European studies, almost all patients (> 99%) identified as white, whereas in the US study, 57% of patients identified as white, 36% identified as Black or African American, and 7% of patients identified as being of other races. In Study 301 and Study 302, 6% and 4% of patients, respectively, had a BMI of 30 kg/m^2 or higher, and in Study 303, patients with a higher BMI made up 35% of the population.

One additional open-label, noncomparative study was included to address gaps in the systematic review evidence. Study 304 (N = 102) provided safety and tolerability data in adolescent patients who received drospirenone 4 mg for 6 cycles in the core study, and up to 7 cycles in the extension study. No indirect evidence or other long-term extension studies were submitted by the sponsor. No data from the desogestrel group in Study 302 were included in this report because this drug is not approved for use in Canada and is not a relevant comparator.

Interpretation of Results

Efficacy

The evidence included in the systematic review was limited to 3 nonrandomized, single-arm studies. Of the efficacy data submitted, the clinical expert consulted by CADTH identified the PI corrected for sexual activity without back-up contraception and the overall PI as the most important outcomes in the trials. This is consistent with regulatory guidance, in which the PI for evaluable cycles is recommended as the primary end point for US contraceptive trials, and the overall PI is recommended as the primary end point for European studies.[33,34]

The studies included in the systematic review from the US (Study 303) and Europe (Study 301 and Study 302) met the criteria specified in regulatory guidance for being considered effective at preventing pregnancy. For the US study, the upper bound of the 95% CI for the PI for evaluable cycles was 4.5 pregnancies per 100 PYs in the overall study population and 5.1 pregnancies per 100 PYs for patients aged 35 years or younger (based on 12 confirmed on-drug pregnancies). These observed values were consistent with FDA guidance that states highly effective COCs typically have a 95% CI upper bound of less than 5, but an upper bound "slightly above" 5 may be acceptable for a product such as a POP.[34] However, the sponsor's primary analyses may not have included all pregnancies. When the 17 confirmed and unconfirmed pregnancies in Study 303 were included in the FDA reanalyses, the upper bound of the 95% CI increased to 6.4 pregnancies per 100 PYs in females aged 35 years or younger.

The European studies reported overall PI point estimates of 0.51 and 0.97 pregnancies per 100 PYs for Study 301 and Study 302, respectively, and a pooled overall PI of 0.73 pregnancies per 100 PYs (95% CI, 0.31 to 1.43). European Medicines Agency guidance states a PI greater than 1 may be considered a "relatively high pregnancy rate."[33]

For all studies, the results in the subgroup of patients aged 35 years or younger were consistent with the findings in the overall study population. In general, the proportion of enrolled patients who were older than

35 years was limited (398 out of 2,577, or 15%), and no pregnancies were reported in this subgroup. Study 303 explored the efficacy of drospirenone in subgroups based on BMI and weight and found no evidence to suggest the PI was higher in patients with higher body mass. All efficacy results were based on patients who were not breastfeeding, and the PI in lactating patients is unclear.

The European studies reported a lower pregnancy rate compared with the US study, although caution is warranted in comparing results between studies, as naive indirect comparisons have a high risk of bias. No studies that enrolled patients from both regions were conducted, and such studies may have helped assess if there were regional variations in efficacy. The CADTH reviewer noted some differences in patient characteristics between the trials based on age, racial distribution, BMI, and VTE risks, but the potential impact of these differences is unclear. The US study showed a high frequency of withdrawals, with only 35% completing 13 cycles of therapy, and more than a quarter of the enrolled patients being lost to follow-up. This withdrawal frequency was higher than expected according to the study's protocol and higher than what was observed in the European studies (from which 20% and 28% of patients withdrew). While the calculation of the PI accounts for study duration, there is some uncertainty as to whether the characteristics of the patients who completed Study 303 remained similar to those of the patients initially enrolled. The PI, as a measure of the pregnancy rate, has been criticized because it will decrease with the duration of a clinical trial.[37] The likelihood of pregnancy decreases over time, as patients most likely to conceive do so earlier and no longer contribute to the follow-up time.[37] A life-table analysis does not share this problem and can be used to calculate the probability of pregnancy for any duration of exposure. In the drospirenone trials, the cumulative pregnancy ratio was 0.7% over 9 cycles in Study 302, and it was 0.5% and 2.0% over 13 cycles in Study 301 and Study 303, respectively. These findings are consistent with those for the PI in the 3 key trials.

Study 301 and Study 303 measured acceptability by asking patients to rate their well-being or satisfaction with drospirenone. At the last study visit, most patients reported a favourable response, with 6% to 14% providing unfavourable responses. Similarly, patients who switched from another hormonal contraceptive generally rated their well-being as being unchanged (42% to 44%), or improved (31% to 33%) with drospirenone, while 14% to 21% reported their well-being was worse. As these data were missing results from 6% and 38% of patients in Study 301 and Study 303, respectively, at the last study visit, the results may not represent the overall enrolled population, particularly for Study 303, as patients with unfavourable tolerability reaction to drospirenone may have been more likely to drop out. Further, the sponsor did not provide any evidence to support the validity and reliability of these questions as a measure of treatment satisfaction, and the clinical expert consulted by CADTH suggested that continuation at 1 year may provide more meaningful results.

Although the sponsor provided a clinical trial of drospirenone in adolescents, this study was designed to assess safety, not contraceptive efficacy, and the PI in younger patients is not known. However, the clinical expert anticipated that drospirenone will have similar treatment effects in adults and adolescents, as these patients are hormonally similar.

Both the sponsor and CADTH identified norethindrone as the key comparator to drospirenone. However, no direct or indirect evidence was submitted for drospirenone versus norethindrone, seriously limiting the ability

to evaluate the comparative efficacy. According to the FDA label, norethindrone has a pregnancy rate of 0.5% in the first year if use is perfect, although the pregnancy rate with typical use is approximately 5%.[38] The Canadian product monograph for norethindrone reports an overall pregnancy rate of 2.5 pregnancies per 100 PYs.[8] Estimates of oral-contraceptive failure rates in the US were unable to distinguish between COCs and POPs, and report a pregnancy rate in the first year of 0.3% to 1% with perfect use, and 9% for typical use.[24] Given the lack of controlled trials, the evidence regarding the effect of drospirenone on contraceptive efficacy and acceptability against any active comparator is very uncertain.

Harms

In the 3 trials included in the systematic review, a total of 2,577 adult patients received drospirenone for up to 1 year. The most common TEAEs were headaches, acne, nasopharyngitis, breast pain nausea, and bleeding-related events. Overall, the frequency of serious TEAEs was low (< 2%), and 10% to 12% of patients discontinued due to adverse events. The frequency of adverse events reported in the study in adolescents (Study 304, N = 102) was similar to those in the adult studies.

Hyperkalemia was listed as an adverse event of special interest because drospirenone is a spironolactone analogue, which has antimineralocorticoid properties and may increase serum potassium levels.[8] Across the studies, 6 patients reported hyperkalemia, with 5 events meeting the threshold of a serious adverse event. All hyperkalemia-related serious adverse events resolved without sequalae (except for 1 event for which the outcome is unknown). The product monograph states that monitoring of serum potassium levels should be considered in females at increased risk for hyperkalemia.[8]

In addition, VTE was identified as an adverse event of special interest as drospirenone containing COCs has been associated with an increased risk of thromboembolism.[39] No VTE adverse events were reported in the 3 key studies, or the safety study in adolescents. All studies excluded patients at high risk of VTE, and only 11 patients who were breastfeeding (who have a higher risk of VTE) were included in the studies. Due to these exclusions, it is not possible to assess the safety of drospirenone in these higher-risk patients.

The clinical expert consulted by CADTH identified bleeding and spotting as a key outcome in the trials. According to the clinical expert, the frequency of bleeding and spotting may be an important factor for patients when selecting a POP. Based on the expert's clinical experience, this may explain why some patients prefer norethindrone over drospirenone. During the 3 adult trials, both scheduled and unscheduled bleeding were common, with 56% to 68% of patients reporting scheduled bleeding, and 68% to 76% of patients reporting unscheduled bleeding during cycle 2 to cycle 4. In the last follow-up period, 38% to 44% of patients reported scheduled bleeding, and 52% to 65% reported unscheduled bleeding. However, the proportion of patients who stopped drospirenone due to bleeding or spotting was generally low (3.3% to 4.9%). The frequency of bleeding and spotting among adolescents in Study 304 was generally similar to that reported in adults. Given the lack of comparative data, it is unclear if bleeding and spotting are more common with drospirenone than with norethindrone.

Overall, the safety data were limited by the duration of the studies (up to 1 year), and the absence of a control group. The trials also excluded patients with comorbidities, such as cardiovascular, renal, or liver

disease; diabetes with vascular involvement; and psychiatric or substance-use disorders, and the safety of drospirenone in these patients is therefore unclear.

Conclusion

Three clinical trials (Study 301, Study 302, and Study 303) in adult females at risk of pregnancy demonstrated the contraceptive efficacy of drospirenone 4 mg over 1 year. This finding was based on results for the overall PI and the PI corrected for sexual activity without back-up contraception that met predetermined therapeutic thresholds for contraceptive efficacy set out by regulatory agencies. During the trials, the majority of patients reported unscheduled vaginal bleeding or spotting. Less than 5% of patients withdrew due to bleeding-related adverse events. No VTE events were reported in the trials, and hyperkalemia TEAEs were infrequent. A supplemental uncontrolled clinical trial in adolescents detected no new safety signals after up to 1 year of drospirenone treatment.

No indirect treatment comparison for drospirenone versus norethindrone was submitted by the sponsor. Given the lack of direct or indirect comparative evidence involving a relevant comparator, no conclusions can be drawn about the efficacy and safety of drospirenone relative to other POPs available in Canada.

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Appendix 1: Detailed Outcome Data

Table 19: Subgroup Analyses for the Pearl Index

Outcomes	Study 301 (FAS Population) Drospirenone (N = 713)	Study 302 (FAS Population) Drospirenone (N = 858)	Study 303 (MFAS Population) Drospirenone (N = 993)
Pearl Index			
Females aged ≤ 35 years			
Number of patients	569	682	915
Overall PI (95% CI)	0.66 (0.14, 1.93)	1.24 (0.40, 2.90)	2.7 (1.4, 4.7)
Corrected PI (95% CI)[a]	0.71 (0.15, 2.06)	1.40 (0.45, 3.27)	NA
PI from evaluable cycles (95% CI)[b]	NA	NA	2.9[c] (1.5, 5.1)
Females aged > 35 years			
Number of patients	144	176	78
Overall PI (95% CI)	NA	NA	0.0 (NC, 6.6)
Corrected PI (95% CI)[a]	NA	NA	(NC, 7.2)
PI from evaluable cycles (95% CI)[b]	NA	NA	0.0 (NC, 11.3)
Body mass index < 30 kg/m^2 [d]			
Number of patients	672	828	641
Overall PI (95% CI)	NA	NA	2.4 (1.0, 4.8)
PI from evaluable cycles (95% CI)[b]	NA	NA	3.0 (1.3, 5.8)[e]
Body mass index ≥ 30 kg/m^2 [d]			
Number of patients	41	30	352
Overall PI (95% CI)	NA	NA	2.3 (0.6; 5.8)
PI from evaluable cycles (95% CI)[b]	NA	NA	2.9 (0.8, 7.3)[e]

Outcomes	Study 301 (FAS Population) Drospirenone (N = 713)	Study 302 (FAS Population) Drospirenone (N = 858)	Study 303 (MFAS Population) Drospirenone (N = 993)
Weight < median[d]			
Number of patients	NR	NR	473
Overall PI (95% CI)	NA	NA	3.4 (1.4, 6.6)
PI from evaluable cycles (95% CI)[b]	NA	NA	4.0 (1.7, 8.0)[f]
Weight ≥ median[d]			
Number of patients	NR	NR	520
Overall PI (95% CI)	NA	NA	1.5 (0.4, 3.8)
PI from evaluable cycles (95% CI)[b]	NA	NA	1.9 (0.5, 4.8)[f]

CI = confidence interval; FAS = full analysis set; NA = not applicable; NC = not calculable; PI = Pearl Index.

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

[a]Corrected PI = Overall PI after correction for additional contraception and sexual activity status

[b]PI for evaluable cycles excludes exposure time where no sexual intercourse occurred or back-up contraception was used.

[c]Data of sites 104 and 120 were excluded from analyses because of serious regulation breaches. The PI from evaluable cycles for ≤ 35 years old including these 2 data sites is 4.0. There is no change in PI from evaluable cycles for > 35 years old because no pregnancies occurred in these sites for this subgroup.

[d]Corrected PI in confirmed and suspected, nonconfirmed pregnancies. For the corrected PI, BMI and weight subgroup were done in females aged ≤ 35 years old.

[e]Data of sites 104 and 120 were excluded from analyses because of serious regulation breaches. The PI from evaluable cycles for BMI < 30 kg/m^2 including these 2 data sites is 4.2. The PI from evaluable cycles for BMI ≥ 30 kg/m^2 including these 2 data sites is 3.5.

[f]Data of sites 104 and 120 were excluded from analyses because of serious regulation breaches. The PI from evaluable cycles for weight < median including these 2 data sites is 4.2. The PI from evaluable cycles for weight ≥ median including these 2 data sites is 1.9.

Note that this table has not been copy-edited.

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] Clinical Study Report for Study 303,[16] and the table are from the sponsor's Summary of Clinical Evidence.

Table 20: Pregnancy Ratio Outcomes

Outcomes	Study 301 (FAS Population) Drospirenone (N = 713)	Study 302 (FAS Population) Drospirenone (N = 858)	Study 303 (MFAS Population) Drospirenone (N = 993)
Pregnancy ratio from exposure cycles[a]			
All females			
Cycle 6			
N	590	714	993
% Cumulative pregnancy ratio (95% CI)	0.30 (0.00, 0.71)	0.40 (0.00, 0.86)	1.42 (0.53, 2.30)
Cycle 9			
N	544	664	NA
% Cumulative pregnancy ratio (95% CI)	0.30 (0, 0.71)	0.70 (0.09, 1.31)	NA
Cycle 13			
N	499	NA	NA
% Cumulative pregnancy ratio (95% CI)	0.50 (0, 1.07)	NA	2.00 (0.79, 3.19)
Females aged ≤ 35 years			
Cycle 6			
N	455	555	915
% Cumulative pregnancy ratio (95% CI)	0.38 (0.00, 0.90)	0.51 (0.00, 1.09)	1.57 (0.59, 2.55)
Cycle 9			
N	414	513	NA
% Cumulative pregnancy ratio (95% CI)	0.38 (0, 0.90)	0.90 (0.11, 1.68)	NA
Cycle 13			
N	383	NA	NA

Outcomes	Study 301 (FAS Population) Drospirenone (N = 713)	Study 302 (FAS Population) Drospirenone (N = 858)	Study 303 (MFAS Population) Drospirenone (N = 993)
% Cumulative pregnancy ratio (95% CI)	0.64 (0, 1.37)	NA	2.24 (0.87, 3.58)
Females aged > 35 years			
Cycle 6			
N	NA	NA	78
% Cumulative pregnancy ratio (95% CI)	NA	NA	0.00 (NC)
Cycle 13			
N	NA	NA	78
% Cumulative pregnancy ratio (95% CI)	NA	NA	0.00 (NC)

CI = confidence interval; FAS = full analysis set; MFAS = modified full analysis set; N = number; NA = not applicable; NC = not calculable.

Note: For Study 301 and 302, the pooled % cumulative pregnancy ratio was 0.72 (0.17 to 1.27) at cycle 13 for the overall population and 0.93 (0.21 to 1.64) for those 35 years of age or younger.

[a]The discreet interval Kaplan-Meier method was used to estimate the cumulative pregnancy ratio (i.e., cumulative pregnancy probability). Logarithmic transformation was used for 95% CI, of the pregnancy ratio.

Note that this table has not been copy-edited.

Sources: Clinical Study Report for Study 301,[14] Clinical Study Report for Study 302,[15] Clinical Study Report for Study 303,[16] and the sponsor's Summary of Clinical Evidence.

Pharmacoeconomic Review

List of Tables

Abbreviations

BIA	budget impact analysis
POP	progestin-only pill

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Drospirenone (Slynd), tablets
Submitted price	Drospirenone, 4 mg tablets: $10.99 per 28-day pack
Indication	For conception control in adolescent and adult females
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	November 30, 2021
Reimbursement request	As per indication
Sponsor	Duchesnay Inc.
Submission history	Previously reviewed: No

NOC = Notice of Compliance.

Table 2: Summary of Economic Information

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	For conception control in females of reproductive potential
Treatment	Drospirenone
Comparator	Norethindrone (Jencycla, Movisse, Maeve)
Perspective	Canadian publicly funded health care payer
Time horizon	1 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., an 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 that the clinical efficacy and safety of drospirenone and norethindrone are similar is uncertain because no direct or indirect comparative clinical evidence was provided to support the assumption. Furthermore, the sponsor assumed that the only relevant comparators for drospirenone are progestin-only pills and did not include oral contraceptives other than norethindrone in the review. The cost-effectiveness of drospirenone compared with oral contraceptives other than norethindrone is therefore unknown. Other oral contraceptives that cost less than drospirenone are available in Canada.

Component	Description
CADTH reanalysis results	• CADTH did not undertake any reanalyses of the sponsor's cost-minimization analysis and emphasized 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 result in no increase to drug plan budgets based on its submitted price relative to the published list price of norethindrone.

Conclusions

Based on the CADTH clinical review, use of drospirenone 4 mg by adult females at risk of pregnancy demonstrated contraceptive efficacy over a year based on the results of 3 clinical trials (Study 301, Study 302, and Study 303). Given the lack of direct or indirect comparative evidence comparing drospirenone to a relevant comparator, no conclusions can be drawn on the comparative efficacy and safety of drospirenone relative to other POPs available in Canada.

The sponsor's cost-minimization analysis assumes that the clinical efficacy and safety of drospirenone and norethindrone are similar. However, given the findings of CADTH's clinical review and the absence of comparative clinical evidence, the validity of the sponsor's cost-minimization analysis is uncertain. If drospirenone is considered to have similar clinical efficacy and safety to norethindrone, and budgets given the equivalent list price, treatment with drospirenone when compared to norethindrone should result in no increase to drug plan. Importantly, other oral contraceptives that are less costly than drospirenone are available in Canada. However, these comparators were not included in the sponsor's analysis and the efficacy and cost-effectiveness of drospirenone compared with oral contraceptives other than norethindrone are unknown.

Economic Review

The current review is for drospirenone (Slynd) for conception control in females of reproductive potential.

Economic Information

Summary of Sponsor's Economic Information

The sponsor submitted a cost-minimization analysis for drospirenone compared with norethindrone for conception control in females of reproductive potential.[1] The modelled population was aligned with the Health Canada indication and reimbursement request. The sponsor assumed that the only relevant comparators for drospirenone are progestin-only pills (POPs) and that these would be used preferentially by people for whom estrogen is contraindicated. Norethindrone is the only other POP currently reimbursed in Canada and the patient population intended to be treated with drospirenone and norethindrone was assumed by the sponsor to be the same.

Drospirenone is available as 4 mg tablets for oral use at a recommended dosage of 1 tablet daily.[2] At the submitted price of $10.99 per 28-day pack, the annual treatment cost of drospirenone was $142.87 per

patient. Norethindrone was also considered at a cost of $10.99 per 28-day pack and the annual treatment cost was the same as that of drospirenone.

The sponsor assumed drospirenone was associated with efficacy and safety similar to norethindrone, based on an editorial letter in published literature.[3] The sponsor adopted dosing as described by the product monographs and assumed 100% adherence in estimating treatment costs.[2,4-6] As a result, all clinical benefits and resource use beyond drug acquisition costs were assumed to be equivalent, and the sponsor's base case considered only drug acquisition costs. The analysis was conducted from the perspective of the publicly funded health care payer over a time horizon of 1 year. As such, discounting was not applied. Based on the sponsor's submission, treatment with drospirenone did not result in any increase to drug plan budgets compared with norethindrone.

The sponsor did not present any scenario analyses.

Table 3: Summary of Sponsor's Economic Evaluation Results

Drug	Total drug costs ($)	Incremental drug costs ($)	Total costs ($)	Incremental costs ($)
Norethindrone	143	Reference	143	Reference
Drospirenone	143	0	143	0

Source: Sponsor's economic submission.[1]

CADTH Appraisal of the Sponsor's Economic Information

CADTH identified a key limitation to the sponsor's analysis that has implications for the economic analysis:

- **The assumption of comparable clinical efficacy and safety between drospirenone and norethindrone is uncertain:** The sponsor submitted no direct or indirect comparative clinical evidence for drospirenone and norethindrone. The sponsor assumed equal efficacy and safety based on a naive comparison of drospirenone and norethindrone in a published editorial letter.[3] The editorial letter narratively compared contraception failure rates and the risk of venous thromboembolism, and noted the similarity of the 2 POPs. However, because no matching-adjusted analysis was performed to correct for imbalances in patient demographics, the results of this comparison are susceptible to confounding through the influence of unmeasured and unadjusted confounders. In the absence of comparative clinical evidence submitted by the sponsor or identified during the review, CADTH sought clinical expert opinion on this matter. Feedback received from the clinical expert supported the assumption of equal efficacy; however, it was suggested that there were differences in spotting incidences between the 2 POPs that can be inconvenient for some users. Ultimately, without any head-to-head or indirect comparison, the sponsor's assumption of equal efficacy and safety is not substantiated with evidence other than expert opinion and is, therefore, uncertain.

  The sponsor did not model any clinical or safety outcomes in the submitted pharmacoeconomic model because the sponsor assumed no differences in long-term outcomes, such as contraception failure rate, bleeding profile, treatment duration, discontinuation, and switching. The sponsor's approach did not allow the reviewers to explore alternative assumptions of comparative efficacy and safety and is, again, unsubstantiated, and uncertain.

Furthermore, the sponsor assumed that the only relevant comparators for drospirenone are POPs and did not include oral contraceptives other than norethindrone in the review. As such, the cost-effectiveness of drospirenone compared with oral contraceptives other than norethindrone is unknown. Importantly, other oral contraceptives that are less costly than drospirenone are available in Canada.[7,8] The clinical expert consulted for this review noted that oral contraceptives containing estrogens would not be commonly used in a population that is using progestin-only oral contraception.

- CADTH was unable to address this limitation due to the lack of comparative evidence.

CADTH Reanalyses of the Economic Information

CADTH did not undertake a base-case reanalysis, as the uncertainty in the comparable clinical evidence could not be addressed. This limited the assessment of the cost-minimization analysis.

If the clinical efficacy and safety of drospirenone and norethindrone are considered similar, reimbursement of drospirenone should not result in any additional drug plan costs compared with norethindrone. This is because drospirenone is priced the same as norethindrone and the recommended dosage is the same for the 2 POPs. The daily and annual costs are equal.

Issues for Consideration

- The product monograph for drospirenone provides administration and dosage guidance for switching to drospirenone from alternative contraceptive methods such as a combined oral contraceptive, transdermal patch, vaginal ring, intrauterine contraceptive, or implant.[2] However, in the absence of comparative clinical evidence, the cost-effectiveness of drospirenone compared with other contraceptive products is unknown. The clinical expert consulted by CADTH anticipated that switching from alternative contraceptive methods to drospirenone would be uncommon in clinical practice.
- Public drug plan input noted that contraceptives are listed for open benefit on public formularies and are prescribed in clinical practice for reasons other than contraception (e.g., acne management). The clinical expert consulted by CADTH also anticipated off-label use of drospirenone if it is reimbursed. However, the budget impact resulting from the use of drospirenone for indications other than the Health Canada indication is outside the scope of this review.
- Both the sponsor's and CADTH's analyses are based on publicly available list prices for norethindrone. At these list prices, reimbursement of drospirenone may result in no increase to drug plan budgets when compared to norethindrone. However, the actual costs paid by public drug plans are unknown.

Conclusions

Based on the CADTH clinical review, use of drospirenone 4 mg by adult females at risk of pregnancy demonstrated contraceptive efficacy over a year based on the results of 3 clinical trials (Study 301, Study 302, and Study 303). Given the absence of direct or indirect comparative evidence comparing drospirenone

to a relevant comparator, no conclusions can be drawn on the efficacy and safety of drospirenone relative to other POPs available in Canada.

The sponsor's cost-minimization analysis assumes the clinical efficacy and safety of drospirenone and norethindrone are similar. However, given the findings of CADTH's clinical review and the absence of comparative clinical evidence, the validity of the sponsor's cost-minimization analysis is uncertain. If the clinical efficacy and safety of drospirenone is considered to be similar to those of norethindrone, and given the equivalent list price, treatment with drospirenone when compared to norethindrone should result in no increase to drug plan budgets. Importantly, other oral contraceptives that are less costly than drospirenone are available in Canada. However, these comparators were not included in the sponsor's analysis and the efficacy and cost-effectiveness of drospirenone compared with oral contraceptives other than norethindrone are unknown.

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Appendix 1: Additional Economic Information

Note that this appendix has not been copy-edited.

Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s) and drug plan. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 4: CADTH Cost Comparison Table for Oral Contraception Use

Treatment	Strength	Form	Price ($)	Recommended dosage	Average daily cost ($)	Average annual cost ($)
Drospirenone (Slynd)	4 mg	28-tablet pack	10.9900[a]	1 pack every 28 days	0.39	143
Progestin-only, oral						
Norethindrone (Jencycla, Maeve, Movisse)[b]	0.35 mg	28-tablet pack	10.9900	1 pack every 28 days	0.39	143

Notes: All prices are from the Ontario Drug Benefit Formulary (accessed September 2023), unless otherwise indicated, and do not include dispensing fees.[8]

The clinical expert consulted for this review noted that oral contraceptives containing estrogens would not be commonly used in the same population that is using progestin-only oral contraception. As such, the estrogen-containing oral contraceptives are not included in this cost table. However, lower cost estrogen-containing oral contraceptives exist in Canada.

[a]Sponsor submitted price.[1]

[b]Other norethindrone brands such as Micronor are not reimbursed in drug programs participating in CADTH's reimbursement review processes.

Additional Details on the Sponsor's Submission

No additional information from the sponsor's submitted pharmacoeconomic evaluation was considered in the review of drospirenone.

Additional Details on the CADTH Reanalyses and Additional Analyses

CADTH did not conduct any additional pharmacoeconomic analyses in the review of drospirenone.

Appendix 2: Submitted Budget Impact Analysis and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 5: Summary of Key Take-Aways

Key take-aways of the budget impact analysis
• CADTH identified the following key limitations with the sponsor's analysis: ◦ 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.

Summary of Sponsor's Budget Impact Analysis

The submitted budget impact analysis (BIA) assessed the expected budgetary impact of reimbursing drospirenone for contraception control in women of reproductive potential.[9] The BIA was undertaken from the perspective of the Canadian public drug plans at base year (2023) and over a 3-year time horizon (2024 to 2026). The sponsor's pan-Canadian estimates reflected the aggregated results from provincial budgets (excluding Québec). Key inputs to the BIA are documented in Table 6.

A claims-based approach was taken to estimate the total market size, in terms of units, for patients currently publicly reimbursed for norethindrone (Jencycla, Movisse and Maeve). The sponsor obtained the total number of units dispensed using the IQVIA Canadian Drugstore and Hospital Database and estimated the number of units dispensed in each jurisdiction by multiplying with the proportion of patients aged 15 to 49 years in each jurisdiction.[10] The sponsor adopted an annual population growth rate of 1.31% and assumed an annual population expansion of 10%.[9, 11,12] The sponsor assumed the coverage rate by public plans would be the same as those reported for individuals aged less than 65 years in a report on Prescribed Drug Spending in Canada published by the Canadian Institute for Health Insurance,[13] to estimate the market size covered by the public health care payer.

The cost of drospirenone was based on the sponsor's submitted price ($10.99 per 28-day pack).[9] Comparators included norethindrone (Jencycla, Movisse, and Maeve). No drug wastage was assumed. Markup and dispensing fees were included and 100% adherence was assumed. Dosage was obtained from respective product monographs.[2,4-6]

Table 6: Summary of Key Model Parameters

Parameter	Sponsor's estimate (year 1 / year 2 / year 3 if relevant)
Target population	
Annual population growth rate	1.31%
Annual population market expansion	10%
Percentage of public coverage	28.2%
Number of patients eligible for drug under review	220,280 / 245,888 / 274,481
Market uptake (3 years)	
Uptake (reference scenario) Jencycla Movisse Maeve	 53.57% / 53.49% / 53.40% 46.27% / 46.19% / 46.12% 0.16% / 0.32% / 0.48%
Uptake (new drug scenario) Drospirenone Jencycla Movisse Maeve	 30.00% / 60.00% / 90.00% 37.50% / 21.39% / 5.34% 32.39% / 18.48% / 4.61% 0.11% / 0.13% / 0.05%
Cost of treatment (per patient)	
Cost of treatment over 28 days	
Drospirenone Slynd	 $10.9900
Norethindrone Jencycla Movisse Maeve	 $10.9900 $10.9900 $10.9900

Summary of the Sponsor's Budget Impact Analysis Results

Results of the sponsor's base case suggest that there is no incremental budget associated with the reimbursement of drospirenone for contraception control in women of reproductive potential (incremental budget impact: $0 in year 1, year 2, and year 3, for a 3-year cumulative budget impact of $0).

CADTH Appraisal of the Sponsor's Budget Impact Analysis

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 to estimate market size introduces uncertainty with the anticipated budget impact of drospirenone:** The sponsor estimated market size based on claims data for the relevant comparators. The sponsor assumed that all public claims for norethindrone are for the indication of interest. However, according to the clinical expert consulted by CADTH for this review,

there is off-label use of norethindrone for menstrual cycle control and abnormal bleeding in women with a contraindication or intolerance to estrogen. Given the claims database does not specify the indication and the proportion of claims pertaining to use for other indications is unknown, using a claims-based approach to estimate market size introduces uncertainty in the estimated market size.

Furthermore, the sponsor did not convert the claims data into the number of users; instead, the sponsor assumed unit to unit displacement between drospirenone and comparators. Given both treatments are delivered in the same dosing regimen and the majority of market uptake comes from a treatment with the same dosing regimen, this is unlikely to have had a significant impact on results. However, for transparency and completeness, claims-based BIAs should provide an estimate of the number of active beneficiaries converted from the number of claims.

- CADTH could not address this limitation.

CADTH Reanalyses of the Budget Impact Analysis

CADTH did not undertake a base case reanalysis, as limitations related to the claims-based approach could not be addressed. The results are presented in Table 7.

These results assume no market displacement of oral contraceptives 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.

Table 7: Detailed Breakdown of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	3-year total
Submitted base case	Reference	$3,630,797	$4,048,822	$4,515,087	$5,035,172	$13,599,081
	New drug	$3,630,797	$4,048,822	$4,515,087	$5,035,172	$13,599,081
	Budget impact	$0	$0	$0	$0	$0

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