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CADTH Reimbursement Recommendation

Ospemifene (Osphena)

Indication: In postmenopausal women for the treatment of moderate to severe dyspareunia and/or vaginal dryness, symptoms of vulvar and vaginal atrophy, a component of genitourinary syndrome of menopause

Sponsor: Duchesnay Inc.

Final recommendation: Reimburse with conditions

CADTH

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

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Osphena?

CADTH recommends that Osphena should be reimbursed by public drug plans for the treatment of postmenopausal women with moderate to severe dyspareunia and/or vaginal dryness, symptoms of vulvar and vaginal atrophy (VVA), a component of genitourinary syndrome of menopause, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Osphena should only be covered for patients who share the same characteristics as patients who are eligible for vaginal estrogen products that are currently reimbursed by public drug plans for the treatment of postmenopausal VVA.

What Are the Conditions for Reimbursement?

Osphena should only be reimbursed if it is not used with other estrogen therapies and if treatment with Osphena does not cost more than treatment with the least costly vaginal estrogen product currently reimbursed for postmenopausal VVA.

Why Did CADTH Make This Recommendation?

- Evidence from 5 clinical trials demonstrated that Osphena improves dyspareunia (painful sex) and vaginal dryness, restores vaginal tissues, and improves vaginal pH levels better than placebo.
- Osphena provides a treatment option for patients who prefer an oral treatment over a local vaginal therapy.
- There is no evidence to show Osphena is more effective than other reimbursed therapies used to treat postmenopausal VVA.
- Osphena will cost the public drug plans an additional $4,294,925 over 3 years.

Additional Information

What Are Dyspareunia and Vaginal Dryness?

Dyspareunia (painful sex) and vaginal dryness are symptoms of VVA, which is when the lining of the vagina thins due to the loss of estrogen after menopause. Approximately 34% of postmenopausal individuals are living with dyspareunia and/or vaginal dryness associated with VVA.

Unmet Needs for Dyspareunia and Vaginal Dryness

Currently available vaginal estrogen therapies are typically effective in providing symptom relief for most patients. Patients with mobility issues may find local vaginal therapies difficult to use. Some patients also may find these therapies very painful to use.

How Much Does Osphena Cost?

Treatment with Osphena is expected to cost approximately $567 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ospemifene be reimbursed for postmenopausal women for the treatment of moderate to severe dyspareunia and/or vaginal dryness, symptoms of vulvar and vaginal atrophy (VVA), a component of genitourinary syndrome of menopause only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 5 double-blind, randomized controlled trials (RCTs) demonstrated that treatment with ospemifene resulted in a clinical benefit for patients with moderate to severe dyspareunia and/or vaginal dryness (symptoms of VVA) compared with placebo. Study 310, Study 821, and Study 231 demonstrated that 12 weeks of treatment with ospemifene was associated with statistically significant improvements compared with placebo for the following: severity of dyspareunia, percentage of vaginal superficial cells, percentage of vaginal parabasal cells, and vaginal pH. Study 310 and Study 231 also demonstrated statistically significant improvements in severity of vaginal dryness with ospemifene compared with placebo. Study 718 and Study 310X provided evidence of safety for up to 52 weeks of treatment with ospemifene. Indirect evidence from 2 network meta-analyses (NMAs) was associated with uncertainty due to heterogeneity, a lack of precision, and other limitations. The NMAs did not support an added clinical benefit with ospemifene compared with other treatments for symptoms of VVA. The clinical expert consulted by CADTH indicated that currently available vaginal estrogen therapies are typically effective in providing symptom relief for most patients. Patients also described variable experience and tolerability of different therapies and the consequent need for additional choice of therapies. Ospemifene may provide an option for patients who prefer oral products over localized vaginal therapies because the latter can be difficult to self-administer, particularly for patients with issues related to mobility or severe pain.

Using the sponsor-submitted price for ospemifene and publicly listed prices for all other drug costs, ospemifene was more costly and less effective compared with local estrogen therapies. Due to uncertainty associated with the comparative clinical efficacy assumptions, ospemifene should be no more costly than the least costly local estrogen therapy for patients with moderate to severe dyspareunia and/or vaginal dryness.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Reimburse in a similar manner to vaginal estrogen products currently funded to treat VVA.	To align with how plans currently reimburse comparators and reconcile any differences that may exist. No evidence was reviewed that supports a clinical benefit for ospemifene compared with other therapies for postmenopausal symptoms of VVA. At the time of this review, vaginal estrogen therapies were identified as the relevant comparators for ospemifene.	—
Prescribing		
2. Should not be used in combination with other estrogens or estrogen agonists or antagonists (as per product monograph).	No evidence was reviewed that examined combination therapy with local or oral estrogen therapy.	—
Pricing		
3. Ospemifene should be negotiated so that it does not exceed the drug program cost of treatment with the least costly local estrogen therapy reimbursed for the treatment of dyspareunia and/or vaginal dryness, which are symptoms of VVA, a component of genitourinary syndrome of menopause.	No evidence was reviewed that supports a clinical benefit for ospemifene compared with other available local estrogen therapies used to treat symptoms of VVA, a component of genitourinary syndrome of menopause. There is insufficient evidence to justify a cost premium for ospemifene over the least costly local estrogen therapy reimburse for VVA.	—

VVA = vulvar and vaginal atrophy.

Discussion Points

- CDEC noted that some patients who are suitable candidates for vaginal estrogen therapies may be hesitant to use these therapies due to contraindications for some patient populations and serious warnings based on evidence from systemic estrogen replacement therapies. However, ospemifene has its own serious warnings for endometrial cancer, stroke, and deep vein thrombosis and has contraindications that include estrogen-dependent neoplasia and arterial thromboembolic disease.
- The clinical expert indicated that vasomotor symptoms are a common symptom in menopausal women, and it is anticipated that many women experiencing menopause may require treatment for both vasomotor and VVA symptoms. The product monograph for ospemifene states that it should not be used in combination with estrogens and estrogen receptor agonists or antagonists. Because ospemifene may increase the risk of

experiencing vasomotor symptoms, vasomotor symptoms should be treated with non-estrogen therapies and lifestyle management.

Background

Ospemifene has been approved by Health Canada in postmenopausal women for the treatment of moderate to severe dyspareunia and/or vaginal dryness, which are symptoms of VVA that is a component of genitourinary syndrome of menopause. Ospemifene is a selective estrogen receptor modulator. It is available as a tablet for oral administration; the dosage recommended in the product monograph is 60 mg once daily with food.

Sources of Information Used by the Committee

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

- a systematic review that included 5 phase III, double-blind, placebo-controlled RCTs in postmenopausal individuals with VVA
- a review of 1 sponsor-submitted NMA and 1 published NMA
- a review of 1 phase III, open-label, long-term safety extension (LTSE) in postmenopausal individuals without a uterus who had VVA
- patients' perspectives gathered by 1 patient group: Women's Health Coalition of Alberta (WHC)
- a summary prepared by CADTH of patients' experiences with menopause and libido, vaginal dryness, dyspareunia, and urinary problems that were obtained from the website Healthtalk.org, a non-profit organization in the UK
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating postmenopausal individuals living with symptoms of VVA
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

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

Patient Input

Input was received from 1 patient group: the WHC. The WHC advocates, raises awareness, and educates about urogynecological and reproductive health of individuals of all ages. The WHC noted the overall lack of awareness and understanding of urogynecological health, the limited therapeutic options for peri- and postmenopausal conditions (e.g.,

postmenopausal VVA), and the potential inequity in accessing preferred treatments if not reimbursed by public drug plans. The WHC emphasized that clinical and psychological impacts caused by untreated menopausal conditions are often overlooked and dismissed. They also expressed that they expected a suitable treatment option for patients would improve health outcomes and potentially raise clinician awareness of the importance of treating menopausal conditions.

To provide additional background on lived experience, values, and preferences of patients with VVA, patient group websites were sought for original experiences of patients with VVA. Healthtalk.org is a non-profit organization that has collected hundreds of stories from patients with any health condition. Information was obtained, assessed, and synthesized by the CADTH review team from video interviews with 13 British patients about VVA that was available through Healthtalk.org. Among the interviewed patients, vaginal dryness, decline in libido contributing to a decline in sexual activity, and urinary problems were reported as some of the common complications experienced after entering menopause. Interviewed patients also described the importance of sex in a marriage and how decreased sexual activity attributed to symptoms of VVA may add significant complications to a relationship over time. During the interview, 1 woman was made aware of her lack of knowledge regarding the effects of hormone replacement therapies, and that treatment with hormone replacement therapies may not prevent the "thinning of the vaginal wall." The thinning of vaginal tissue was reported as causing severe discomfort for many patients, resulting in vaginal tears and bleeding. Patients also described how the decline of estrogen they had experienced affected the pelvic floor, the bladder, the womb, the vagina, and bowel leading to urinary and bowel problems. Patients also reported difficulty with incontinence; the negative impact on quality of life was experienced by many other patients.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of postmenopausal patients with VVA.

The clinical expert indicated that individuals with VVA will typically present with vaginal dryness, pruritis, burning or pain, and dyspareunia, and the goal of treatment is to provide relief of these symptoms. In the experience of the clinical expert, currently available treatments are effective in providing relief of symptoms of VVA in most cases. Because most available treatments for symptoms of VVA are administered intravaginally, ospemifene offers an alternative route of administration as an orally administered tablet; however, the clinical expert also noted that some patients may prefer a local therapy over systemic therapy due to hesitancy around the use of hormonal treatments.

The clinical expert consulted for this review noted that despite the utility of vaginal moisturizers and/or lubricants, women with VVA will generally experience more effective symptomatic relief from vaginal local estrogen. The clinical expert noted that, more recently, additional therapeutic options have become available for the treatment of genitourinary syndrome of menopause, such as intravaginal prasterone and orally administered ospemifene (a selective estrogen receptor modulator), which represent a departure from traditional estrogen-based management strategies and substantially widen the scope of options available to women with VVA. The clinical expert relayed that the main adverse effect of ospemifene is hot flashes, which they felt may be a significant barrier to widespread use in

women with postmenopausal symptoms. The clinical expert suggested that after taking this and other factors into account, it is unlikely that ospemifene will become first-line therapy.

The clinical expert consulted for this review felt that the majority of patients with genitourinary syndrome of menopause are anticipated to benefit from a therapeutic agent with estrogen receptor agonist properties, such as ospemifene. Feedback from the expert indicated that patients most in need of intervention are those with more severe symptoms, and ospemifene provides an additional option to traditional vaginal estrogen therapy. Additionally, the clinical expert felt that the oral route of administration for ospemifene may be especially suited for women who are unable to self-administer vaginal medication, such as due to severe pain or mobility limitations.

The clinical expert stated that women who do not report symptoms would generally not be diagnosed with symptoms of VVA in clinical practice and that patients will generally self-identify based on description of symptoms on clinical history. Alternatively, patients seen for urogynecologic issues such as vaginal prolapse or urinary incontinence may have VVA identified at the time of assessment by history and visual inspection. The expert noted that clinical history and visual inspection of the vulva on physical examination would be usual methods for identification of patients with VVA; however, with the rise in telemedicine, the expert anticipates that more diagnoses will be made on clinical history alone, which may also be considered a reasonable approach.

The clinical expert did not identify a specific subgroup of patients that would be less suited for treatment with ospemifene beyond those with any contraindication to ospemifene.

The clinical expert consulted by CADTH indicated that, in clinical practice, subjective patient-reported improvement in symptoms is the primary outcome used to determine whether a patient is responding to treatment. The expert noted that improvement of symptoms is most often correlated with visual inspection at examination, although subjective symptoms are clinically more meaningful than appearance. Moreover, any improvement in vulvovaginal symptoms would be considered a clinically meaningful response according to the clinical expert, who noted this may include decrease in sensation of vaginal dryness, decreased vaginal burning and/or pain, decreased frequency of urinary tract infections or bladder urgency and/or irritation, and decreased dryness and pain during intercourse. Histologic examination is generally not performed or required based on the experience of the clinical expert.

Based on feedback from the clinical expert, there is no strict schedule for when treatment response needs to be assessed. The expert suggested that it would be reasonable to assess response to treatment approximately 3 months to 6 months after initiation of treatment, again at 6 months to 12 months, and yearly thereafter.

Regarding discontinuation of treatment, the clinical expert consulted by CADTH stated that a patient may choose to discontinue treatment, although symptoms may return after some time. The clinical expert noted that assessment of the risks and benefits is subjective because, ultimately, the goal of treatment is improved quality of life.

The clinical expert indicated that ospemifene would most likely be prescribed in an outpatient ambulatory clinic setting by a family physician or gynecologist, and that patients would self-administer the medication at home. Genitourinary syndrome of menopause is very common;

therefore, the clinical expert felt that most clinicians with experience in the treatment of women's health issues would be suitable prescribers for pharmacologic treatment.

Clinician Group Input

Input was not received from clinician groups for the review of ospemifene.

Drug Program Input

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for continuation or renewal of therapy	
In the long-term studies, compared with placebo, there were no significant estrogen-related or clinically important AEs affecting the endometrial or breast tissue in patients treated with ospemifene over 52 weeks; however, the product monograph indicates that Osphena is a medicine that works like estrogen in the lining of the uterus and may increase the chance of endometrial cancer. Should consideration be given to monitoring parameters (e.g., endometrial sampling in the event that breakthrough bleeding or spotting occurs)?	The clinical expert indicated that endometrial sampling, most commonly by endometrial biopsy, is generally required in patients with postmenopausal bleeding, and this would be especially important in patients taking medication with agonist effects on the uterus, such as estrogen, tamoxifen, and ospemifene. CDEC agreed with the clinical expert that an endometrial biopsy would be done in the event of bleeding and did not expect it to be a routine part of care when prescribing this product.
Considerations for discontinuation of therapy	
Consideration should be given to discontinuation criteria in the event of thromboembolic or hemorrhagic stroke.	CDEC considered this issue in their deliberations but felt discontinuation due to thromboembolic or hemorrhagic stroke would be a clinical decision and it is also aligned with the product monograph.
Considerations for prescribing of therapy	
Has consideration been given to the concomitant use of other medications for the treatment of hot flashes resulting from the use of Osphena? As per the product monograph, Osphena should not be used concomitantly with estrogens and estrogen receptor agonists or antagonists. The safety of concomitant use of Osphena with estrogens and estrogen receptor agonists or antagonists has not been studied.	The clinical expert indicated that vasomotor symptoms are a common symptom in menopausal individuals, and it is anticipated that many individuals may require treatment for both vasomotor symptoms and vulvovaginal symptoms. Because ospemifene should not be used with other estrogens or estrogen agonists or antagonists, this limits its use in individuals with concomitant vasomotor symptoms; increased vasomotor symptoms from the use of ospemifene is a further complicating consideration. Ospemifene may still be used in individuals who are using non–estrogen-based therapies for vasomotor symptoms, including antidepressants, gabapentinoids, clonidine, oxybutynin, and lifestyle management strategies. CDEC did not have any further comments to add.

Implementation issues	Response
Generalizability	
Genitourinary syndrome of menopause describes various menopausal symptoms and signs associated with physical changes of the vulva, vagina, and lower urinary tract. Genitourinary syndrome of menopause includes not only genital symptoms (dryness, burning, and irritation) and sexual symptoms (lack of lubrication, discomfort or pain, and impaired function), but also urinary symptoms (urgency, dysuria, and recurrent urinary tract infections). Has consideration been given to using Osphena for non-vaginal symptoms because it is a systemic drug vs. a locally administered product (e.g., Vagifem, Premarin)?	The clinical expert indicated that ospemifene is used for genitourinary symptoms of menopause as described above, noting that it is not used for systemic symptoms of menopause, such as vasomotor symptoms. Further, the use of ospemifene has been shown to be associated with an increase in vasomotor symptoms of menopause. CDEC did not have any further comments to add.
System and economic issues	
Sponsor expects that Osphena will displace market share primarily from Vagifem. However, Vagifem is not funded in British Columbia or by VAC.	CDEC considered this issue in their deliberations.
Consideration may be given to the cost of treatment of hot flashes and urinary tract infections resulting from treatment with Osphena.	CDEC considered this issue and acknowledged that addressing hot flashes or urinary tract infections may result in switching or discontinuation of treatment.
Confidential negotiated prices may exist for Vagifem, Premarin, and Estring. If there is a lack of evidence to demonstrate superiority of Osphena vs. comparators, consideration should be given to a pricing condition indicating that drug plan cost for Osphena not exceed the drug plan cost of least costly vaginal estrogen product.	CDEC considered this issue in their deliberations.

AE = adverse event; CDEC = CADTH Canadian Drug Expert Committee; VAC = Veterans Affairs Canada; vs = versus.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

A total of 5 phase III, double-blind, placebo-controlled RCTs that assessed ospemifene 60 mg were included in the systematic review: Study 310 (N = 544, excluding the ospemifene 30 mg treatment group), Study 821 (N = 919), Study 231 (N = 631), Study 718 (N = 426), and Study 310X (N = 118, who continued from Study 310). Study 310, Study 821, and Study 231 were designed to assess the efficacy and safety of ospemifene 60 mg over 12 weeks, Study 718 was designed to assess the efficacy and long-term safety of ospemifene 60 mg over 52 weeks, and Study 310X was a 52-week LTSE of Study 310 that only assessed safety outcomes. The trials were conducted between 2006 and 2009 (Study 310, Study 821, and Study 718), except for Study 231 which was conducted between 2016 and 2017. Primarily, the trials recruited patients in the US; no patients were studied in Canada. All of the studies enrolled postmenopausal individuals between 40 years and 80 years of age, who had 5% or fewer superficial cells in the maturation index of the vaginal smear, and vaginal pH greater

than 5.0. In addition, Study 310, Study 821, and Study 231 included patients who identified at least 1 moderate to severe symptom of VVA considered the most bothersome. Study 310, Study 821, Study 231, and Study 718 included the following as co-primary end points assessed at week 12: percentage of vaginal superficial and vaginal parabasal cells on a vaginal smear and vaginal pH. Study 310, Study 821, and Study 231 also included severity of the most bothersome symptom (MBS) of VVA as a co-primary end point. Secondary end points assessed in 12-week studies included urinary symptoms using the Urinary Distress Inventory Short Form (UDI-6) and sexual function (only Study 821 and Study 231) using the Female Sexual Function Index (FSFI). Health-related quality of life, mental health–related outcomes, bone mineral density, and adherence were identified as outcomes of interest to this review but were not assessed in any of the included studies. The majority of patients included in Study 310, Study 821, Study 231, and Study 718 were 55 years of age or older and White. The proportion of patients that had previous experience with hormonal treatment varied significantly between the studies (ranging from 3% to 61% of patients). Of the 544 patients in Study 310, 222 (41%) reported vaginal dryness as the MBS and 242 (44%) reported vaginal pain with sexual activity (dyspareunia) as the MBS. In Study 821, 314 (34%) patients reported vaginal dryness as their MBS and 605 (66%) reported dyspareunia as their MBS. In Study 231, patients were required to have vaginal dryness as their MBS; Study 718 did not report assessments of MBS at baseline. Baseline characteristics for Study 310X were limited to demographic information.

Efficacy Results

Efficacy of ospemifene was assessed in 4 of the 5 included studies (all except Study 310X). A summary of key efficacy results follows.

The change in severity of symptoms of VVA following 12 weeks of treatment was measured using the VVA questionnaire and evaluated in Study 310, Study 821, and Study 231 as a co-primary end point. The VVA questionnaire is a patient-reported assessment of the severity of symptoms of VVA. Patients are asked to indicate the severity of the most severe episode using a 4-point scale, in which none, mild, moderate, or severe correspond to a score of 0, 1, 2, or 3, respectively. A formal minimal important difference (MID) was also not identified in the published literature; however, the clinical expert consulted by CADTH indicated that any reduction in symptom severity was considered clinically meaningful because it is 1 of the primary goals of treatment. Each of these studies evaluated the change in vaginal dryness in patients who identified it as the MBS of VVA. In Study 310, the mean change in severity of the vaginal dryness at week 12 was −1.26 (standard deviation [SD] = 1.03) and −0.84 (SD = 1.00) for the ospemifene and placebo treatment groups, respectively, indicating patients randomized to ospemifene reported a greater reduction in symptom severity compared with patients randomized to placebo (P = 0.021). [redacted] All patients included in Study 231 reported moderate or severe vaginal dryness as the MBS of VVA at baseline. The mean change in symptom severity from baseline to week 12 was −1.29 (SD = 1.01) for ospemifene and −0.91 (SD = 0.96) for placebo (P < 0.0001). In Study 821, change from baseline in vaginal dryness was assessed in the dryness stratum (patients indicating vaginal dryness as the MBS of VVA at baseline). In contrast to the results of Study 310 and Study 231, Study 821 did not demonstrate a statistically significant difference in the reduction of severity of vaginal dryness compared with placebo based on a mean difference of −1.3 (SD = 1.08) for ospemifene and −1.1 (SD = 1.02) for placebo (P = 0.080) at week 12. Given the failure to demonstrate an improvement

based on vaginal dryness as the MBS of VVA, efficacy of ospemifene could not be concluded in the dryness stratum.

Patients who identified dyspareunia as the MBS of VVA were also enrolled in Study 310 and Study 821. In Study 310, this included 142 of 544 (26%) patients from the overall ITT population. This population informed the analysis of the change from baseline to week 12 in severity of dyspareunia as the MBS of VVA, as part of the co-primary end point for severity of the MBS of VVA. In Study 310, the mean change from baseline to week 12 in severity of dyspareunia was −1.2 (SD = 1.3) in the ospemifene treatment group and −0.9 (SD = 1.1) in the placebo treatment group, which corresponded to a greater reduction in the severity of dyspareunia with ospemifene compared with placebo (P = 0.023). In Study 821, the co-primary end points in the dyspareunia stratum were analyzed independent of the dryness stratum. In Study 821, the mean change from baseline in severity of dyspareunia was −1.5 (SD = 1.08) in the ospemifene treatment group and −1.2 (SD = 1.12) in the placebo treatment group. Therefore, a greater reduction in the severity of dyspareunia with ospemifene compared with placebo was demonstrated (P = 0.0001).

Measurements of cytology included the percentage of parabasal cells and the percentage of superficial cells from a vaginal smear. The change from baseline to week 12 in the percentage of parabasal cells and superficial cells were co-primary end points in Study 310, Study 821, Study 231, and Study 718. These outcomes provide an objective assessment of the signs of VVA and are considered standard in clinical trials; however, the clinical expert consulted by CADTH indicated they are not particularly relevant to clinicians because they are rarely assessed in clinical practice. A reduction in the percentage of parabasal cells and an increase in the percentage of superficial cells correspond to an improvement in VVA. Study 310, Study 821 (dryness stratum and dyspareunia stratum), Study 231, and Study 718 demonstrated a reduction in the percentage of parabasal cells and an increase in the percentage of superficial cells in favour of ospemifene compared to placebo. These outcomes are not typically used in clinical practice; therefore, the clinical expert was unable to quantify a clinically meaningful improvement in these outcomes. Further, a formal MID was not identified in the published literature.

The change from baseline to week 12 in the percentage of parabasal cells and the percentage of superficial cells were reported as follows:

- In Study 310, the mean change from baseline in the percentage of parabasal cells was −30.1% (SD = 37.93%) and 3.98% (SD = 35.21%) for the ospemifene and placebo treatment groups, respectively, in favour of ospemifene (P < 0.001). The mean change in the percentage of superficial cells was 10.8% (SD = 15.66%) for the ospemifene group and 2.18% (SD = 8.39%) for the placebo group, in favour of ospemifene (P < 0.001).
- In Study 231, the least squares (LS) mean change in the percentage of parabasal cells was −23.7% (standard error [SE] = 1.4%) and −1.9% (SE = 1.4%) for the ospemifene and placebo treatment groups, respectively, in favour of ospemifene (treatment group difference = −21.8%; 95% confidence interval [CI], −25.7% to −18.0%; P < 0.0001). The LS mean change in the percentage of superficial cells was 7.8% (SE = 0.7) and 0.6% (SE = 0.7%) for the ospemifene and placebo treatment groups, respectively, in favour of ospemifene (treatment group difference = 7.2%; 95% CI, 5.2% to 9.1%; P < 0.0001).
- In the dryness stratum of Study 821, the LS mean change in the percentage of parabasal cells was −31.7% (SE = 2.11%) for ospemifene and −3.9% (SE = 2.18%) for placebo (treatment group difference = −27.8%; 95% CI, −33.75% to −21.90%; P < 0.0001). The

change in the percentage of superficial cells was reported as a median (range) because the ANCOVA assumptions were not met. The median change at week 12 was 7.0% (range = −4% to 65%) for ospemifene and 0.0% (range = −11% to 57%) for placebo, in favour of ospemifene (P < 0.0001).

- In the dyspareunia stratum of Study 821, the LS mean change in the percentage of parabasal cells for ospemifene and placebo was −40.3% (SE = 1.56%) and −0.4% (SE = 1.57%), respectively (treatment group difference = −39.9%; 95% CI, −44.15% to −35.63%; P < 0.0001). The change in the percentage of superficial cells was reported as a median (range) because the ANCOVA assumptions were not met. The median change at week 12 was 7.0% (range = −6% to 79%) for ospemifene and 0.0% (range = −5% to 85%) for placebo, in favour of ospemifene (P < 0.0001).
- A non-parametric method for analysis was used in Study 718 because the assumptions of ANCOVA were not met. The median of the change in the percentage of parabasal cells was −40% (95% distribution-free CI, −55.0% to −30.0%) for ospemifene and 0% (95% distribution-free CI, 0.0% to 10.0%) for placebo, in favour of ospemifene (P < 0.0001). The median of the change in the percentage of superficial cells was 5% (95% CI, 5.0% to 7.0%) for ospemifene and 0% (95% CI, 0.0 to 0.0) for placebo, in favour of ospemifene (P < 0.0001).

Study 718 also assessed the percentage of parabasal cells and superficial cells at week 26 and week 52 as secondary outcomes. The results of both outcome assessments were similar to the results at week 12; however, the study was not powered to detect a difference in secondary outcomes, and they were not controlled for multiplicity.

Vaginal pH was assessed in Study 310, Study 821, Study 231, and Study 718 as the change from baseline to week 12. This was a co-primary end point in each of the 4 studies. Similar to cytology assessments, vaginal pH is often measured in clinical trials, but it is not particularly relevant to clinicians because it is rarely assessed in clinical practice. The clinical expert consulted by CADTH was unable to quantify a clinically meaningful improvement in vaginal pH, and a formal MID was not identified in published literature. However, vaginal pH greater than 5.0 is an indicator of vaginal atrophy; therefore, a reduction in pH is suggestive of an improvement in VVA.

- In Study 310, the mean change from baseline to week 12 in vaginal pH was −1.0 (SD = 1.1) for ospemifene and −0.1 (SD = 08) for placebo, in favour of ospemifene (P < 0.001).
- In Study 231, the LS mean change from baseline to week 12 was −1.01 (SE = 0.04) for ospemifene and −0.29 (SE = 0.04) for placebo, corresponding to a treatment group difference of −0.72 (95% CI, −0.84 to −0.59; P < 0.0001) in favour of ospemifene.
- In Study 821, the LS mean change from baseline to week 12 in vaginal pH was −0.95 (SE = 0.07) and −0.94 (SE = 0.05) for ospemifene in the dryness and dyspareunia strata, respectively. The LS mean change from baseline in the placebo treatment groups was −0.25 (SE = 0.07) and −0.07 (SE = 0.05) in the dryness and dyspareunia strata, respectively. The difference in the change in vaginal pH was in favour of ospemifene for both strata (P < 0.0001).
- In Study 718, the mean change from baseline to week 12 in vaginal pH was −1.21 (SD = 0.912) for ospemifene and −0.16 (SD = 0.945) for placebo, corresponding to a treatment group difference of −0.97 (95% CI, −1.17 to −0.77; P < 0.0001) in favour of ospemifene. The analyses at week 26 and week 52 were based on observed cases, which yielded similar results to those reported at week 12.

- Urinary symptoms were assessed as a secondary outcome using the UDI-6 in Study 310 and Study 821 by domain score and total score, and by the total score in Study 231. No change in urinary symptoms, as measured by the UDI-6, were observed in any of the analyses. Sexual function was assessed as a secondary outcome in Study 821 and Study 231 using the FSFI. The FSFI is commonly used in clinical trials and is a validated tool for measurement of women's overall sexual function. The clinical expert consulted by CADTH indicated that the domains the FSFI assesses are clinically relevant, but sexual function is typically evaluated informally in clinical practice. Overall, the results of the FSFI were inconsistent between studies or did not demonstrate an improvement in sexual function compared with placebo, except for the pain domain. The treatment group difference in the change in score from baseline to week 12 for the pain domain was 0.58 (95% CI, 0.327 to 0.838) in Study 821 (all patients) and 0.45 (95% CI, 0.11 to 0.80) in Study 231, which suggested an improvement in favour of ospemifene. This result is aligned with a reduction in severity of dyspareunia demonstrated in the trials.

Harms Results

In all of the included studies, no deaths were reported; specific serious adverse events (SAEs) were infrequently reported. No SAEs were reported by patients who received ospemifene in Study 310; 1.5% of patients who received placebo reported at least 1 SAE. The proportion of patients reporting at least 1 SAE in Study 821 and Study 231 were similar between treatment groups (1.3% versus 1.5% in Study 821 and 1.6% versus 1.0% in Study 231 for ospemifene versus placebo). In Study 718, 4.9% of patients in the ospemifene group and 6.5% of patients in the placebo treatment group reported at least 1 SAE. During the 12-week treatment period, patients who received ospemifene reported adverse events (AEs) at a similar or slightly higher frequency than patients who received placebo in Study 310 (60% vs. 52%, respectively), Study 821 (63% and 51%, respectively), and Study 231 (35% vs. 33%, respectively). Similar results were observed during the 52-week treatment period of Study 718, although the frequency of AEs was higher overall than in the 12-week studies. AEs were reported more frequently by those who received ospemifene compared with placebo (64% versus 45%) during the 52-week treatment period of Study 310X (including 12 weeks in Study 310), although this is likely biased in favour of placebo due to the high rate of discontinuation from study in the placebo treatment group. Specific AEs were not reported in more than 9% of patients in the 12-week studies or 13% of patients in Study 718, but the most commonly reported AE in each of the 4 studies was hot flashes. Hot flashes were consistently reported more frequently by patients who received ospemifene (6% to 8% of patients who received ospemifene and 3% to 3% of patients who received placebo). Vaginal infections, vaginal discharge, and muscle spasms were also commonly reported AEs that were more frequent with ospemifene than placebo. Overall, patients who withdrew from treatment due to an AE were similar between treatment groups in the 12-week trials (2% to 5% for ospemifene and 3% to 5% for placebo). In Study 718 and Study 310X, withdrawal from treatment due to an AE was more frequent in the ospemifene treatment groups (14% and 6%, respectively) than placebo (10% and 2%, respectively). The rates of specific AEs leading to discontinuation were infrequent; however, in every study, hot flashes were the only AE that led to treatment discontinuation for at least 1 patient who received ospemifene.

The following notable harms were included in the CADTH systematic review protocol: vaginal hemorrhage, abnormal genital bleeding, cervical dysplasia, breast mass, endometrial hyperplasia, uterine polyps, cardiovascular disorders (e.g., thromboembolic and hemorrhagic stroke, coronary heart disease), breast cancer, uterine cancer, deep vein thrombosis, and pulmonary embolism. In Study 310, Study 821, Study 231, and Study 718, a total of [redacted] in

the ospemifene treatment groups and [redacted] in the placebo treatment groups reported vaginal hemorrhage. Uterine polyps were reported by 6 patients and 1 patient for ospemifene and placebo, respectively. Cervical dysplasia was reported in [redacted] for ospemifene and [redacted] for placebo and breast mass was reported in 7 patients from both the ospemifene treatment groups and placebo treatment groups. Endometrial hyperplasia was reported in 1 patient who received ospemifene, and breast cancer was reported in 1 patient who received placebo. A total of 2 patients reported deep vein thrombosis, both in the ospemifene treatment groups. No patients reported experiencing abnormal genital bleeding, uterine cancer, pulmonary embolism, or other cardiovascular disorders (e.g., thromboembolic and hemorrhagic stroke, coronary heart disease). In Study 310X, vaginal hemorrhage (n = 1), cervical dysplasia (n = 1), and breast mass (n = 1) were reported in the ospemifene treatment group. No other notable harms were reported.

Critical Appraisal

Each of the studies used a mix of objective clinical outcomes and subjective patient-reported outcomes. Objective outcomes included cytology assessments (percentage of parabasal cells and percentage of superficial cells) and vaginal pH, which are based on clinical results obtained from a vaginal smear. Although commonly used in clinical trials, the objective outcomes are not typically used in clinical practice, as per feedback from the clinical expert. Subjective outcomes were patient-reported and included the VVA questionnaire to assess the symptoms of VVA, the UDI-6 to assess urinary symptoms, and the FSFI to assess sexual function. Although the clinical expert consulted by CADTH indicated that the self-reported outcomes are considered clinically relevant in practice to measure treatment response, published MIDs were not identified for these outcome measures in postmenopausal individuals. Therefore, it is unclear whether the reported between-group differences are clinically meaningful. Further, evidence of validity, reliability, and responsiveness of the VVA questionnaire was not identified for this review along with the validity of treating the ordinal data as continuous, which makes it is difficult to interpret the results. Additionally, secondary outcomes (UDI-6, FSFI, and any outcomes reported after week 12) were not controlled for multiplicity and are therefore subject to type I error.

In all studies, the primary efficacy analyses were performed using the ITT population, and supportive analyses were performed in the per-protocol (PP) population and mITT population (Study 231 only). All of the supportive analyses performed were consistent with the primary analyses, with the exception of vaginal dryness as the MBS of VVA in Study 310 where statistical significance was not demonstrated in the PP population. The sponsor attributed the lack of statistical significance for the supportive analysis to the small sample size, which is likely a contributing factor; however, the results of the analysis of vaginal dryness as the MBS of VVA in Study 310 remains uncertain.

In Study 718, patients with VVA were identified based on the maturation index and vaginal pH, without a requirement for self-reported symptoms of VVA. This introduces uncertainty about the generalizability of the patient population to postmenopausal patients with moderate to severe vaginal dryness or dyspareunia. Otherwise, the eligibility criteria used in the included studies were generally considered appropriate and reflective of postmenopausal patients with VVA, although restrictive (70% of patients in Study 231 failed screening; data were not reported in the other included studies). Most notably, patients with comorbidities such as a history of cancer or cardiovascular disorders were excluded from the trials, leading to uncertainty regarding the generalizability of the safety results. Evidence informing the efficacy of ospemifene is primarily based on patients receiving treatment for up to 12 weeks.

Supportive efficacy data based on clinical outcomes was available for up to 52 weeks; however, the evidence is weak and not based on clinically relevant outcomes (symptom severity) causing uncertainty in the long-term efficacy. Safety evidence in patients who received treatment for up to 52 weeks was available, but subject to high and imbalanced discontinuation rates. Moreover, patients are expected to continue treatment for more than 1 year and evidence of safety beyond this time point is unknown.

Indirect Comparisons

Description of Studies

The sponsor-submitted ITC was included in this review and an additional ITC by Li et al. identified in the literature search. Both of the ITCs conducted a systematic review and NMA to evaluate the comparative efficacy and safety of ospemifene to other alternative therapies in the treat of VVA. Both ITCs used a Bayesian framework for NMA analysis.

In the sponsor-submitted ITC, 27 RCTs were eligible, 5 of which involved ospemifene. Other treatments investigated included conjugated estrogens vaginal cream (Premarin), estradiol vaginal insert (Vagifem), estradiol softgel vaginal insert (Imvexxy), estradiol vaginal ring (Estring), and prasterone vaginal ovule (Intrarosa). The sample size of the included trials ranged from 21 to 826 patients and the mean age from 56 years to 63 years. The eligible RCTs primarily recruited postmenopausal women with moderate to severe genitourinary symptoms, and the majority of the trials were 12 weeks in duration (range = 12 to 14 weeks). For the NMA, the sponsor only included RCTs with the following treatments: ospemifene 60 mg oral daily (Osphena), estradiol vaginal cream 0.02 mg (Estrace), estradiol transdermal patch 14 mcg (Estradiol patch), estradiol vaginal cream 2 and 7.5 mg (Estring), estriol vaginal pessary 0.5 mg (Estriol pessary), estradiol vaginal capsule 4 mcg and 10 mcg (Imvexxy), DHEA vaginal suppository 6.5 mg (Intrarosa), lubricants, conjugated estrogens vaginal cream 0.3 mg or 0.63 mg (Premarin), promestriene vaginal cream 10 mg, or estradiol vaginal insert 10 mcg (Vagifem). The sponsor noted that the majority of trials were at low risk of bias, although 4 RCTs were at high risk of bias from blinding.

In the ITC by Li et al., 29 RCTs were eligible with 8,311 participants (sample sizes ranged from 180 to 909 patients). Five treatments were investigated: laser therapy, vaginal estrogen (vaginal estrogen therapies pooled together), ospemifene, vaginal DHEA, and moisturization and/or lubrication. The mean age of participants ranged from 51 years to 65 years and the duration of the trials ranged from 6 weeks to 52 weeks. The severity or duration of symptoms was not described by the authors.

Efficacy Results

Sponsor-Submitted ITC

For the outcome of mean difference in the change from baseline to follow-up in MBS score for vaginal dryness, [redacted]

For the outcome of mean difference in change from baseline to follow-up in MBS score for dyspareunia, [redacted]

For the outcome of mean difference in change from baseline to follow-up for combined MBS score for vaginal dryness and dyspareunia, [redacted]

For the outcome of mean difference in change in percentage of parabasal cells, [redacted]

For the outcome of mean difference in change in percentage of superficial cells, [redacted]

For the outcome of mean difference in reduction of vaginal pH, [redacted]

Li et al. ITC

In the ITC by Li et al., there was no difference between ospemifene and vaginal estrogens for the outcomes of mean difference in change in vaginal dryness (mean difference = −2.9; 95% credible interval [CrI], −13 to 8.1), dyspareunia (mean difference = 8.0; 95% CrI, 0.2 to 17), or sexual function (mean difference = 1.5; 95% CrI, −2.7 to 5.6). The reduction in vaginal pH was smaller for ospemifene versus vaginal estrogens (mean difference = 0.31; 95% CrI, 0.05 to 0.58). There was no difference for reduction in percentage of parabasal cells for ospemifene compared with vaginal estrogens (mean difference = 2.2; 95% CrI, −9.5 to 15).

Harms Results

In the sponsor-submitted ITC, there was no difference in the risk of TEAEs for ospemifene versus conjugated estrogens vaginal cream (relative risk [RR] = 1.07; 95% CrI, 0.93 to 1.24) or versus estradiol vaginal tablet (RR = 1.11; 95% CrI, 0.95 to 1.28). There was no difference in the risk of serious TEAEs for ospemifene versus conjugated estrogens vaginal cream (RR = 0.75; 95% CrI, 0.02 to 31) or versus estradiol vaginal tablet (RR = 0.87; 95% CrI, 0.15 to 4.17). There was no difference in risk of UTI between ospemifene and estradiol vaginal tablet (RR 2.55; 95% CrI, 0.23 to 35). The risk of headaches was lower for ospemifene compared with estradiol vaginal ring (RR = 0.00; 95% CrI, 0.00 to 0.04), while there was no difference compared with conjugated estrogens vaginal cream (RR = 0.74; 95% CrI, 0.38 to 1.42) or estradiol vaginal tablet (RR = 1.43; 95% CrI, 0.24 to 8.50). There was no difference in risk of discontinuation due to AEs for ospemifene versus estradiol vaginal ring (RR = 1.26; 95% CrI, 0.28 to 1.52), conjugated estrogens vaginal cream (RR = 0.97; 95% CrI, 0.31 to 2.69), or estradiol vaginal tablet (RR = 0.94; 95% CrI, 0.31 to 2.45).

Critical Appraisal

The sponsor-submitted ITC provided a clear rationale and objective and was generally well conducted aside from the following limitations of note. Heterogeneity in effect sizes (based on $I^2 > 50\%$) was observed for some comparisons; however, was not further explored via meta-regression with suspected effect modifiers. The extent to which eligible studies satisfied the similarity assumption was unclear. Although patient and study characteristics were broadly similar, the appropriateness of combined different doses in nodes, different placebos across trials, and unclear extent of prior VVA treatment make it challenging to assess the similarity of the eligible studies. Subgroup or sensitivity analyses did not result in different results than the base case and were generally not able to explain heterogeneity, although

decisions regarding the methodology were not adequately described. In the analysis of safety outcomes, there were wide CrIs and low event rates (resulting in extremely low RRs) for some comparisons, which makes it challenging to assess the comparative safety (e.g., for headache, urinary tract infection). Further, for some efficacy outcomes, there were a limited number of trials for some nodes, resulting in wide and overlapping CrIs. This makes it difficult to draw conclusions around comparative efficacy for ospemifene and relevant comparators.

The Li et al. ITC described the study objective and study selection process. Concerns were identified with respect to study selection. Specific eligibility criteria were not provided (e.g., based on severity of symptoms) and the authors did not provide explicit criteria around specific relevant interventions or comparators. Information about disease severity or duration of symptoms was not extracted, making it challenging to assess whether the similarity assumption was satisfied. Further, since severity of symptoms was not provided, it is unclear how relevant the population was for the present review. The authors transformed continuous outcomes to a 0 to 100 scale as different outcome scales were used across studies; however, they did not provide details around how this was carried out or whether it was appropriate. Not all comparators in the Li et al. ITC were relevant to this review. The comparison of ospemifene to vaginal estrogens was relevant. However, the Li et al. ITC combined all vaginal estrogens into 1 node (including different drugs and dosage forms, e.g., conjugated estrogens, estradiol 4 mcg or 10 mcg vaginal capsule). Some of the vaginal estrogens included in vaginal estrogen node were not comparators of interest for this review (e.g., estriol cream). Given there may be differences between different vaginal estrogen products in terms of efficacy and safety, the appropriateness of combining these treatments into 1 node is uncertain. It further makes it challenging to draw conclusions around the comparative efficacy and safety of ospemifene to individual relevant treatments. A description of model fit was not provided so it is unclear if model fit was adequate. Network diagrams were not provided in the Li et al. ITC and it was unclear how many studies contributed to specific comparisons. Heterogeneity (I^2 > 50%) was observed for some outcomes involving ospemifene (dyspareunia, vaginal pH, parabasal cells), which could be explained by age (vaginal pH) or dose (change in percentage of parabasal cells) but could not be explained for other outcomes.

Other Relevant Evidence

Description of Studies

Study 312, which is a multi-centre, open-label, phase III, LTSE of Study 310, has been summarized to provide additional evidence regarding the long-term safety of oral daily doses of ospemifene 60 mg for the treatment of VVA in postmenopausal women without a uterus. During this extension study, all patients received ospemifene 60 mg/day irrespective of the treatment assignment in the initial 12-week Study 310. The duration of treatment was 52 weeks followed by a 4-week post-treatment follow-up period, totalling to 68 weeks (including the initial 12-week of Study 310). The baseline characteristics of those who continued into the LTSE were similar to those in the core study based on age, race, ethnicity, and BMI.

Of the 826 postmenopausal women randomized to Study 310, 301 (36.4%) enrolled in the open-label extension study, Study 312. Overall, 117 (38.7%) patients discontinued from the study. The most common reasons for discontinuation were patient decision or withdrawal of consent (13.2%), AEs (12.3%), and lost to follow-up (5.6%).

Efficacy Results

Efficacy was not assessed in Study 312.

Harms Results

During the 52-week treatment period, 73.1% of patients reported at least 1 treatment-emergent AE during the study and 4% of patients reported at least 1 SAE. The most common AEs were sinusitis (8%), urinary tract infection (8.6%), and hot flashes (10.3%). None of the specific SAEs were reported in more than 2 patients. Adverse events leading to treatment discontinuation were reported for 34 (11.3%) patients, with hot flashes reported by 2% of patients being the most frequent AE leading to discontinuation. [redacted] breast mass (n = 1), and hemorrhagic stroke (n = 1) were the only notable harms reported in Study 312, all of which were infrequent.

Critical Appraisal

Study 312 had several limitations imposed by the overall design; the lack of a comparison group to provide context and control for potential confounders. Additionally, the open-label design may influence the perception of improvement by patients and clinicians which could impact the reporting of harms. Among the enrolled patients, 117 (38.7%) discontinued prematurely from the study, which may have resulted in safety outcomes being reported. Since the patients who took part in Study 312 were originally from the parent studies and the eligibility criteria remained the same, it is reasonable to expect that the same limitations to generalizability are relevant to the OLE study. For instance, since the participants were predominantly White (92.4%), the results from these trials may not be generalizable in other racial groups, which may be commonly seen at some centres in Canada. Since this OLE safety study focuses on a very specific patient population, which is postmenopausal women with no uterus, it would be best to compare the safety results with similar studies to have more accurate idea about the safety profile among general population. The treatment duration was 52 weeks, which might not give sufficient time frame to observe and note all potential safety issues.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Postmenopausal patients for the treatment of moderate to severe dyspareunia and/or vaginal dryness, symptoms of vulvar and vaginal atrophy, a component of genitourinary syndrome of menopause.
Treatment	Ospemifene plus SOC (defined as over-the-counter lubricants and moisturizers)
Submitted price	Ospemifene, 60 mg, tablets: $1.5540 per tablet
Treatment cost	At the submitted price of $1.5540 per 60 mg tablet ($139.86 per 90-count bottle or $46.62 per 30-count pack), the annual cost of ospemifene is $567.

Component	Description
Comparator	A mixed basket of local ETs (Premarin and Estragyn vaginal creams, Vagifem vaginal insert and Estring slow-release ring) plus SOC
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	10 years
Key data source	Efficacy data were obtained from an NMA of direct and indirect evidence for ospemifene and local ETs
Key limitations	• There is no difference in the comparative efficacy of ospemifene to local estrogen therapies, as observed in the combined most bothersome symptoms score results of the sponsor's submitted NMA. Several limitations of the NMA used for the model's clinical efficacy inputs result in difficulty drawing conclusions on the comparative clinical efficacy and safety of ospemifene compared to local estrogen therapies. • Treatment discontinuation rates were highly uncertain as they were based on US claims data, which may not reflect treatment discontinuation in the Canadian setting and may overestimate persistence with ospemifene, thus overestimating incremental QALY gain and costs. • Health state utility values used in the economic model are highly uncertain due to the use of naïve assumptions and mapping to derive utility values (i.e., assuming VVA symptom severity is transferable to the MRS, and mapping the MRS to EQ-5D-3L scores). • The sponsor inappropriately compared ospemifene to local ETs by using a mixed basket comparator of local ETs instead of directly comparing to each local ET. The weighted average drug cost was based on the market share of individual treatments, but jurisdictional utilization may vary, thus adding uncertainty to the average drug cost. Additionally, the sponsor overestimated the costs of conjugated estrogen cream and an estradiol ring.
CADTH reanalysis results	• CADTH undertook reanalyses that included assuming no difference in clinical efficacy between ospemifene and local estrogen therapies (i.e., mean combined MBS score reduction); assuming treatment discontinuation rates are the same for all treatments; and revising the list prices of conjugated estrogen creams and the estradiol ring. • Based on CADTH reanalyses, ospemifene was dominated (i.e., more costly [incremental costs: $175] and less effective [incremental QALYs: 0.001]) by local estrogen therapies. A reduction of 93% in the price of ospemifene would be required for ospemifene's to be considered cost-neutral to the lowest cost local ET. • Importantly, while the comparative clinical effectiveness and safety data indicates that there is no difference between ospemifene and currently available standard of care treatments, this should be interpreted with caution due to uncertainty associated with the sponsor-submitted NMA.

ET = estrogen therapy; MRS = Menopause Rating Scale; NMA = network meta-analysis; QALY = quality-adjusted life-year; SOC = standard of care.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the annual treatment discontinuation rate likely underestimated total drug costs of ospemifene based on data that did not reflect Canadian clinical practice; there is uncertainty around the estimates used to determine the size of the population eligible for treatment with ospemifene, which likely led to an underestimation of the population size; the anticipated market uptake of ospemifene is uncertain; and the lowest publicly listed prices for conjugated estrogen cream and the estradiol ring were not selected amid the variation in their list prices across jurisdictions. CADTH estimated a revised base case which included revising the proportion of patients estimated to receive drug coverage, applying a constant treatment discontinuation rate for all treatments, and revising the prices for conjugated estrogen cream and the

estradiol ring based on the lowest publicly listed prices. The estimated budget impact from the reimbursement of ospemifene would be $720,551 in year 1, $1,428,525 in year 2, and $2,221,110 in year 3, for a total incremental budget impact of $4,370,185 over the 3-year time horizon.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: March 23, 2022

Regrets: One expert committee member did not attend.

Conflicts of interest: None