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CADTH Reimbursement Recommendation

Estradiol and Progesterone Capsule (Bijuva)

Indication: For the treatment of moderate-to-severe vasomotor symptoms associated with menopause in women with an intact uterus

Sponsor: Knight Therapeutics Inc.

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

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 Bijuva?

CADTH recommends that Bijuva be reimbursed by public drug plans for the treatment of patients with moderate-to-severe vasomotor symptoms (VMS) associated with menopause if certain conditions are met.

Which Patients Are Eligible for Coverage?

Bijuva should only be covered to treat patients who have moderate-to-severe VMS associated with menopause and have an intact uterus.

What Are the Conditions for Reimbursement?

Bijuva should be reimbursed in a similar way to Bijuva's individual components and all other forms of oral hormone replacement therapy (HRT) and should only be reimbursed if the cost of Bijuva provides savings for the drug plans relative to the cost of treatment with estradiol and progesterone as individual components.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial showed that Bijuva lowered the frequency and severity of moderate-to-severe VMS in patients who are menopausal with an intact uterus, improved health-related quality of life (HRQoL) measures specific to menopause, improved sleep quality, and overall disease severity.
- Based on public list prices, Bijuva will cost the public drug plans less than the combination of its individual components (estradiol and progesterone).
- Based on public list prices, the 3-year budget savings associated with Bijuva is $358,330.

Additional Information

What Are the VMS Associated With Menopause?

VMS are the primary symptoms of menopause and include profuse heat, sweating, hot flushes, and night sweats. Approximately 60% to 80% of patients experience these symptoms during the menopausal transition. Approximately 20% of VMS are of severe intensity, and patients report up to 20 to 30 episodes daily.

Unmet Needs in VMS Associated With Menopause

Clinical experts identified the need for a treatment that improves patient satisfaction.

How Much Does Bijuva Cost?

Treatment with Bijuva is expected to cost the public drug plans approximately $327 per patient, per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that estradiol and progesterone capsule (estradiol-progesterone) be reimbursed for the treatment of moderate-to-severe vasomotor symptoms (VMS) associated with menopause in patients with an intact uterus only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, randomized, double-blind, placebo-controlled trial (the REPLENISH VMS substudy; n = 766) demonstrated that treatment with estradiol-progesterone resulted in a clinically meaningful benefit for patients with an intact uterus who experienced moderate-to-severe VMS during menopause. The REPLENISH VMS substudy demonstrated that estradiol-progesterone significantly improved (i.e., decreased) the frequency and severity of VMS (coprimary end points) at 4 and 12 weeks from baseline in both active treatment groups (1 mg estradiol/100 mg progesterone and 0.5 mg estradiol/100 mg progesterone) compared to placebo. Clinically meaningful improvements were also observed for key secondary end points, including the proportion of patients achieving a 50% or greater and 75% or greater reduction in the frequency of moderate and severe VMS from baseline to week 12, HRQoL measures specific to menopause, sleep quality, and scores for Clinical Global Impression (CGI), a measure of overall disease severity and change, which all favoured treatment with estradiol-progesterone.

No patient input was received for this submission, but the clinical expert indicated that estradiol-progesterone may improve patient satisfaction by offering the convenience of 1 capsule versus taking each component separately. These issues were not addressed in the submitted evidence and therefore CDEC could not determine whether estradiol-progesterone fulfills this need. However, CDEC acknowledged that the treatment goals of HRT are to reduce the frequency and severity of VMS and improve patient quality of life, and that estradiol-progesterone achieves these goals based on the submitted evidence.

Using the sponsor-submitted price for estradiol-progesterone capsules and publicly listed prices for all other drug costs, estradiol-progesterone capsules were less costly compared with its individual component products (estradiol and progesterone).

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Estradiol-progesterone does not require any specialized initiation criteria and should follow existing initiation criteria used for its individual components and all other forms of oral HRT.	No evidence was reviewed to support added clinical benefit for estradiol-progesterone compared with other HRT for this indication.

Reimbursement condition	Reason
Pricing	
2. Estradiol-progesterone capsules should be negotiated so that it provides cost savings to drug programs relative to the cost of treatment of estradiol and progesterone as individual components reimbursed for the treatment of moderate-to-severe VMS associated with menopause in patients with an intact uterus.	At the submitted price, estradiol-progesterone capsules were cost saving in comparison with the regimen of estradiol and progesterone administered as individual components.
Feasibility of adoption	
3. The feasibility of adoption of estradiol-progesterone must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimates.

HRT = hormone replacement therapy; VMS = vasomotor symptoms.

Discussion Points

- CDEC discussed that evidence from the REPLENISH VMS substudy showed consistent clinically meaningful benefit compared to placebo for multiple outcomes despite the large placebo effect that was observed. The clinical expert indicated that a placebo effect is expected and commonly seen in clinical practice for this indication and is partly attributable to natural evolution of the disease and statistical artifact (i.e., regression toward the mean).
- CDEC noted that similar to other trials of HRT, the REPLENISH trial excluded patients with baseline characteristics known to have contraindications to HRT, including a history of thrombosis, coronary artery disease, cardiovascular disease, and cancer.
- CDEC discussed that currently reimbursed bioidentical formulations of HRT (i.e., estradiol and micronized progesterone) for the treatment of moderate-to-severe VMS for patients who are postmenopausal and have an intact uterus are administered as individual components. CDEC also discussed that there was no direct or indirect evidence submitted comparing the estradiol-progesterone capsule to publicly reimbursed HRT options used in this patient population. Therefore, the potential benefit of the estradiol-progesterone capsule compared to other publicly reimbursed HRT in Canada is unknown.
- CDEC noted that the VMS substudy was short (i.e., 12 months) for the assessment of longer-term safety outcomes, particularly those that are correlated with length of time on treatment.

Background

Estradiol-progesterone has a Health Canada indication for treating patients with an intact uterus experiencing moderate-to-severe VMS during menopause. Estradiol-Progesterone is an HRT that is available as a fixed-dose combination of 17Beta estradiol (estradiol hemihydrate)

and progesterone (micronized) in 2 capsule presentations for oral administration (0.5 mg/100 mg and 1 mg/100 mg).

Sources of Information Used by the Committee

To make its recommendation, CDEC considered the following information:

- a review of 1 randomized double-blind, placebo-controlled trial in patients who were postmenopausal, between 40 and 65 years of age, and had an intact uterus
- a summary prepared by CADTH of patients' experiences with menopause and VMS obtained from Healthtalk.org, a non-profit organization in the UK
- input from public drug plans that participate in the CADTH review process
- one clinical specialist with expertise diagnosing and treating patients with menopause and VMS
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

No patient groups submitted input for this review. However, to provide background on patients lived experiences, values, and preferences, and to build an understanding of what it is like to experience moderate and severe hot flushes, patient group websites were sought for original experiences from patients with VMS. Information from Healthtalk.org was obtained, assessed, and synthesized by the CADTH review team. Healthtalk.org is a non-profit organization containing hundreds of real people's stories collected by academic researchers who interview people in their own homes. From this source, the topic of hot flushes and sweats (VMS) was searched, and the results obtained were summarized.

Patients interviewed by experts expressed how symptoms of menopause affect their daily lives. Office and workplace rules and interactions are usually affected, as well as family life, as menopause does not occur in isolation. Family dynamic changes and balancing work and life with moderate-to-severe symptoms represent an important challenge for patients and their families. Furthermore, concerns about family, relationships, work, and finances add uncertainty and anxiety to the burden and stress patients feel around menopause. Many patients described how on many occasions it is impossible to get a good night's sleep during menopause, due to hot flushes and sweats. Patients spoke about the "horrendous" effect of hot sweats on their sleep, of sleeping erratically and being woken up to a "dozen times a night." Waking up feeling hot one minute, cooling down, dozing off to sleep only to be woken up again by a hot sweat can be a vicious sleep-wake-sleep-wake cycle; 1 patient expressed that "you're working nine to five and you need a good night's sleep and [night sweats] certainly did make me feel erratic." Patients in the interviews described their hot flushes vividly, as a "creeping sensation" that rises from the feet through the whole body; an "explosion" in the chest and neck that goes "right up to your brow;" "a thermometer going up and down."

There was no specific experience described on Healthtalk.org with the estrogen-progesterone (Bijuva) medication. However, those who were interviewed talked about their experiences with HRT of any kind, expressed feelings about its risks and benefits, and concerns about

long-term use. In the interviews, experts expressed how a proportion of patients decide not to take HRT due to the media coverage in 2009 and 2010 related to the risks of using HRT, particularly on the increased risk of breast cancer. Others who were interviewed indicated that they feel like they had no choice but to take HRT. Among those who took HRT, the intervention was described as being "like a miracle," "completely rejuvenating," "unfailingly excellent," and "the most wonderful drug in the whole wide world." Deciding to take HRT and to stay on it long-term involves a careful weighing of risks versus benefits; and patients emphasized the need for a complete shared decision-making process. When discussing the length of treatment with HRT, while some patients were willing to discontinue HRT, others were reluctant to stop taking the medication despite their doctor's advice. Many patients were concerned with coming off "cold turkey" and returning to the undesirable features associated with stopping their medication. Other patients stated how weaning slowly over a period of time helped them to come off the medication without any withdrawal symptoms.

Input From the Clinical Expert Consulted by CADTH

The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of VMS associated with menopause.

An important unmet need expressed by the clinical expert consulted by CADTH was the lack of combination products available in Canada that can potentially increase adherence and ease of administration. Even when the expert considered that the new combination of estradiol-progesterone would not necessarily shift the treatment paradigm, they indicated that it may provide a better option for some patients, especially with the convenience of using 1 tablet, rather than taking them separately; this may improve adherence and patient satisfaction. Currently, other available options include conjugated equine estrogen, estradiol, medroxyprogesterone acetate, and norethindrone. For patients with a higher risk for venous thromboembolism (VTE) or stroke or in those with high triglycerides, a transdermal approach to estrogen therapy is preferred.

VMS are usually treated pharmacologically by trialling both hormonal and non-hormonal options. Combined estrogen and progesterone therapies (in 1 or 2 products) are considered by clinicians the most effective treatment options for VMS in patients who have a uterus. HRT does not modify the underlying disease mechanism for VMS, but it provides symptomatic relief. This improves productivity at work and decreases burden of disease for VMS and mood symptoms. The clinical expert indicated that treatment goals are mainly to reduce the severity of symptoms and improve quality of life. The clinical expert highlighted the importance of having a range of doses available to titrate appropriately for a patient to improve symptoms and again when titrating down when appropriate (after a period of stabilization). Although estrogen therapy provides the majority of the treatment effect, a progesterone or progestin is required to protect the uterus from lining overgrowth that may lead to endometrial hyperplasia or carcinoma.

According to the clinical expert, the efficacy of the estrogen-progesterone capsule is expected to be similar to other HRT options in terms of reduction of VMS. Currently, the choice for estrogen-progesterone capsule versus other HRT depends on access in terms of drug plan benefits, intolerance of higher doses of progesterone, and patient preference. The estradiol-progesterone combination may be more ideal for those patients with a higher risk for VTE or stroke, or those who wish to improve their glycemic profile, high-density and low-density lipoproteins cholesterol. Many clinicians prefer micronized progesterone as this component is perceived to have a better safety profile than progesterone. It is always necessary to discuss

with patients the possible benefits and risks of using HRT, especially in those with high cardiovascular risk, diabetes, and older populations.

The clinical expert considered that a reduction of at least 50% in the frequency and severity of VMS would be a meaningful effect. This includes improvements in sleeplessness, work productivity, and mood. Reassessment of patients with VMS should be performed initially after 2 to 4 months of starting treatment, then again after 6 months, and then every 1 to 2 years, but this may vary among physicians. The factors that physicians should consider when deciding whether to discontinue treatment with estradiol-progesterone include side effects to medication that can't be improved by titrating dose, no significant improvement in symptoms despite adequate doses and adherence, and development of other disease process. Discontinuation will also be based on patient preferences and a shared decision process with their physicians.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for estradiol-progesterone:

- relevant comparators
- considerations for initiation of therapy
- generalizability of trial populations to the broader populations in the jurisdictions.

CDEC weighed evidence from the REPLENISH VMS substudy and other clinical considerations, including input from the clinical expert consulted by CADTH, to provide responses to the drug programs' implementation questions, which are presented in Table 2.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
No head-to-head trials with standard of care were presented (i.e., Bijuva vs. placebo in all study designs). The drug plans would have liked to see: • a comparison against a synthetic progesterone • different therapy strategies • daily dose as well as pulse dosing for patients with an intact uterus and last monthly period less than 1 year ago.	CDEC noted that the available evidence is limited to one placebo-controlled trial (REPLENISH) that demonstrated that estradiol-progesterone was superior in reducing the frequency and severity of VMS. CDEC acknowledged that while the selection of HRT may be based on patient preference for a more convenient regimen, there is no direct or indirect evidence to inform on the comparative efficacy and safety of estradiol-progesterone vs. publicly reimbursed HRT options.
Considerations for initiation of therapy	
The following efficacy measures were used in the pivotal study: CGI, MENQOL (validated in Canada), and MOS-Sleep. In Canadian clinical practice, Canadian family physicians use the MQ6.	CDEC agreed with the clinical expert that the efficacy measures used in the pivotal study are validated and those mentioned by the drug plans are also well known among Canadian physicians; therefore, it is unlikely there will be difficulties in applying any of these tools in clinical practice.

Implementation issues	Response
Eligibility criteria and treatment initiation criteria used in the pivotal study are similar to what is used in Canadian clinical practice: • **Inclusion**: Women 40 to 65 years old who are postmenopausal with serum estradiol level less than or equal to 50 pg/mL defined as: amenorrhea greater than or equal to 12 months or greater than or equal to 6 weeks post bilateral oophorectomy or 6 months amenorrhea FSH 40 mIU/mL. BMI less than 34. • **Exclusion**: History of VTE; history of CAD or cerebrovascular disease, CRF, diabetes, thyroid or endocrine disease, estrogen receptor-positive breast cancer, or uterine fibroids or ablation; history of malignancy in the past 5 years; history of other cardiovascular, hepatic, renal, pulmonary, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, psychological (e.g., bipolar disorder, schizophrenia, major depressive disorder), or musculoskeletal disease or disorder that was clinically significant in the opinion of the principal investigator or medical subinvestigator.	CDEC agreed with the clinical expert that the inclusion and exclusion criteria used in the pivotal study are generally similar to what would be used in clinical practice.
Considerations for continuation or renewal of therapy	
No considerations for continuation, renewal, or discontinuation of therapy were identified. Prior therapies were not required for eligibility; however, the investigators had protocols to wean off therapies before initiating treatment. Outcomes were reported on symptom improvement and clinical impression.	CDEC agreed with the clinical expert that no specific criteria exist for continuation of estradiol-progesterone.
Considerations for discontinuation of therapy	
No considerations for discontinuation of therapy were identified.	CDEC agreed with the clinical expert that no specific criteria exist for discontinuation of estradiol-progesterone. Discontinuation is usually based on clinical assessment and baseline risks (e.g., CVD risk, stroke, cancer) and the decision to stop estradiol-progesterone should be made on a case-by-case basis.
Considerations for prescribing of therapy	
No considerations for prescribing of therapy were identified.	CDEC agreed with the clinical expert that prescribing and monitoring patients on estradiol-progesterone does not require specialized expertise.

Implementation issues	Response
Generalizability	
In terms of generalizability, there was a low representation of patients of Asian descent in the pivotal study. Patients in the study with CVD risk factors were excluded and HRT is not necessarily contraindicated in these patients.	CDEC acknowledged there was low representation of patients of Asian descent in the REPLENISH trial but agreed with the clinical expert that this is unlikely to affect the generalizability of the trial results. Similarly, CDEC agreed that patients at high risk for CVD will generally not be considered for HRT. Only a minority of patients with CVD risk factors would be offered HRT, and this should be based on an individual decision-making process between the physician and patient that considers benefits against risks of therapy.

BMI = body mass index; CAD = coronary artery disease; CDEC = Canadian Drug Expert Committee; CGI = Clinical Global Impression; CVD = cardiovascular disease; CRF = chronic renal failure; FSH = follicle stimulating hormone; HRT = hormone replacement therapy; MENQOL = Menopause specific quality of life; MOS = medical outcomes study, MQ6 = Menopause Quick 6; VMS = vasomotor symptom; vs. = versus; VTE = venous thromboembolism.

Clinical Evidence

Pivotal Studies

Description of Studies

REPLENISH Trial

The CADTH clinical review was based on a summary of evidence provided by the sponsor, which included 1 randomized controlled trial that assessed the efficacy and safety of the estradiol-progesterone capsule for patients (40 to 65 years old) experiencing menopause with moderate-to-severe VMS. After the screening of 5,020 patients, a total of 1,845 patients were eligible for inclusion in the REPLENISH trial. Within this eligible population, patients could be included in 2 substudies based on further clinical eligibility criteria:

- The VMS substudy included patients, who at enrolment, had moderate-to-severe VMS (i.e., a minimum daily frequency of ≥ 7 episodes per day [or ≥ 50 per week] of moderate-to-severe hot flushes of VMS). These patients were randomized 1:1:1:1 to 1 of 4 estradiol-progesterone doses (1 mg/100 mg, 0.5 mg/100 mg, 0.5 mg/50 mg, and 0.25 mg/50 mg) or placebo (5 arms in total) and participated in the VMS substudy for the first 12 weeks of treatment.
- The non-substudy included patients who otherwise qualified for the REPLENISH trial but did not report the required minimum daily frequency of moderate-to-severe hot flushes and were randomized to 1 of 4 active treatment groups for 12 months and did not participate in the VMS substudy.

All patients in the REPLENISH trial, including the VMS substudy and the non-substudy patient populations, received a blinded investigational product for 12 months.

The VMS substudy population, which was the basis for the data used to support the Health Canada approval, is the focus of this review. It included a total of 766 patients randomized to 4 active treatment groups or placebo. Meanwhile, the non-substudy included 1,079 patients randomly assigned to 4 active treatment groups, but not placebo. In this review,

the VMS substudy population was used to analyze the coprimary efficacy end points using the data from dosages approved in Canada (i.e., the 1 mg/100 mg and the 0.5 mg/100 mg). The REPLENISH trial provides information about safety end points using the overall safety population and the endometrial safety population (N = 990 for the 1 mg/100 mg and N = 675 for the 0.5 mg/100 mg). The endometrial safety population included all randomized patients who had taken at least 1 capsule of the study treatment, had no major protocol violations, and had an acceptable biopsy at baseline and at month 12.

The VMS substudy includes the modified intention-to-treat VMS population with 141 patients in the estradiol-progesterone 1 mg /100 mg group, 149 patients in the 0.5 mg/100 mg group, and 135 patients in the placebo group.

The coprimary efficacy end points evaluated in the VMS substudy included the mean change in frequency and severity of moderate-to-severe VMS from baseline to week 4 and week 12. Patients recorded hot flush frequency and severity up to week 12 in daily diaries. Hot flush severity was defined as mild, moderate, or severe. Secondary end points included the proportion of patients with a 50% or greater reduction in frequency of moderate-to-severe VMS from baseline at each week up to week 12; the CGI distribution (number and percentage of patients) at weeks 4, 8, and 12, with mean change in the frequency of moderate-to-severe VMS from baseline summarized by different categories of change based on the CGI; and a responder analysis based on responder groups obtained by an anchor based on the CGI. HRQoL was assessed using the change from baseline in the Menopause-Specific Quality of Life Questionnaire (MENQOL) and Medical Outcomes Study (MOS)-Sleep questionnaire.

Patients in the REPLENISH trial were evaluated for safety end points for up to 360 days (double-blind phase). The primary safety end point was the incidence of endometrial hyperplasia with the estrogen-progesterone combination at 12 months. The secondary safety end point was the number of adverse events (AEs). Also, the population was evaluated. Although efficacy analyses were performed at 12 weeks, patients in the VMS substudy continued taking medication for 12 months for their potential inclusion in the endometrial safety population.

Bioequivalence

Two initial bioequivalence single-dose pharmacokinetic studies compared the bioavailability of the estradiol-progesterone capsule 2 mg/200 mg with the same doses of Estrace (estradiol tablets USP) and Prometrium (progesterone USP) in healthy, adult patients who are postmenopausal. In 1 of these studies, Study 351, administration of the study drug was under fasting conditions, while in the other study, Study 352, the study drug was administered 30 minutes after the start of a high-fat, high-calorie meal. Under fasting conditions (i.e., Study 351), the progesterone exposure for the estradiol-progesterone capsule was significantly lower than the reference for all primary pharmacokinetic parameters. However, under high-fat fed conditions (i.e., Study 352), all of the primary pharmacokinetic parameters for progesterone, as well as other parameters for estradiol and its metabolites, were higher for the estradiol-progesterone capsules than the reference.

Due to the intrasubject coefficient of variation being greater than 30% in many cases, a reference-replicated, reference-scaled, bioequivalence approach was taken in Study 459 (the main bioequivalence submission in this review) under high-fat, high-calorie fed conditions. Results showed that estradiol, estrone (free and total), and progesterone plasma concentrations were bioequivalent to the same doses of Estrace and Prometrium under high-fat fed conditions. While the 2 mg estradiol/200 mg progesterone capsule strength is not

being proposed for marketing authorization, the capsule fill contains the same ingredients in the same proportions as the 1 mg/100 mg capsule strength and was manufactured using a comparable process. Therefore, the US FDA and Health Canada judged it to be representative of the commercial product. As such, the dosing recommendation included in the estrogen-progesterone product monograph is to take the capsule each evening with food.

Efficacy Results

REPLENISH VMS Substudy

For the weekly frequency of VMS episodes, both estradiol-progesterone dosages (1 mg/100 mg and 0.5 mg/100 mg) significantly reduced the number of moderate-to-severe VMS when compared to placebo. At week 4, the mean change (standard deviation [SD]) from baseline in the number of weekly moderate and severe VMS was −40.6 (30.59) in the 1 mg/100 mg group, −35.1 (29.14) in the 0.5 mg/100 mg group, and −26.4 (27.05) in the placebo group. The least square (LS) mean change (standard error [SE]) versus placebo was statistically significant in both active treatment groups (−12.81 [3.30] and −8.07 [3.25] with $P < 0.001$ and $P < 0.013$, respectively). At week 12, the mean change (SD) from baseline was maintained with −55.1 (31.36), −53.7 (31.93), and −40.2 (29.79) fewer weekly VMS episodes, respectively, and the LS mean change (SE) versus placebo was statistically significant in both active treatment groups at −16.58 (3.44) and −15.07 (3.39) in the 1 mg/100 mg and the 0.5 mg/100 mg groups, respectively ($P < 0.001$ for both comparisons).

Similarly, for severity of VMS, the severity of symptoms decreased from baseline in both active treatment groups. At week 4, the mean change (SD) from baseline in the severity of symptoms was −0.48 (0.547), −0.51 (0.563), and −0.34 (0.386) in the 1 mg/100 mg, the 0.5 mg/100 mg, and placebo groups, respectively, and the LS mean change (SE) versus placebo was statistically significant in both active treatment groups (−0.13 [0.06] and −0.17 [0.06] with $P = 0.031$ and $P = 0.005$, respectively). At week 12, the mean change (SD) from baseline was maintained with a reduction in the severity of symptoms of −1.12 (0.963), −0.90 (0.783), and −0.56 (0.603) in the active treatment and placebo groups, respectively, and the LS mean change (SE) versus placebo was statistically significant in both active treatment groups at −0.57 (0.10) and −0.39 (0.09) in the 1 mg/100 mg and the 0.5 mg/100 mg groups, respectively ($P < 0.001$ for both comparisons).

A responder was defined as a patient with 50% or greater and 75% or greater reduction from baseline in the number of moderate and severe VMS, performed at week 4 and week 12. In both active treatment groups, a statistically significant difference was observed compared to placebo. At week 12, 79.0% and 80.6% of patients in the 1 mg/100 mg and 0.5 mg/100 mg groups, respectively, had a 50% or greater reduction in the number of moderate and severe VMS compared with 58.3% in the placebo group; and 67.7% and 58.1% of patients in the 1 mg/100 mg and 0.5 mg/100 mg groups, respectively, had a 75% or greater reduction compared with 32.2% in the placebo group.

For the CGI analysis at week 12, the percentage of patients who reported "very much improved" or "much improved" was 82.1% and 72.9% in the 1 mg/100 mg and 0.5 mg/100 mg groups, respectively, compared to 53.4% in the placebo group. At all time points, a statistically significant improvement in both active treatment groups was observed compared to placebo. Based on the nonparametric discriminant analysis, the threshold for reporting a meaningful decrease in weekly moderate-to-severe VMS, based on the best discrimination between patients who reported "minimally improved" and those patients who reported "much or very much improved," was a decrease of 39 VMS at week 12. Based on this definition, 91 (73.4%),

94 (72.9%), and 60 (52.2%) patients in the 1 mg/100 mg, 0.5 mg/100 mg, and placebo groups were responders (P < 0.001).

At week 12 and months 6 and 12, statistically significant improvements (reductions) in the MENQOL Total Score were observed for both active treatment groups compared to placebo. For instance, at month 6, the MENQOL score mean change (SD) from baseline was −2.0 (1.22), −1.8 (1.22), and −1.6 (1.31) in the 1 mg/100 mg, 0.5 mg/100 mg, and placebo groups, respectively (P < 0.001 for both comparisons to placebo).

When evaluating the MOS-Sleep score, at months 6 and 12, statistically significant improvements were noted for both active treatment groups compared to placebo (P < 0.05), except for the 1 mg/100 mg group at month 12 (P = 0.058).

Harms Results

The safety population (N = 1,835) included randomized patients from the VMS substudy and the non-substudy populations (i.e., the overall study population) who took at least 1 dose of the medication. The endometrial safety population (all patients randomized to active treatment who completed 12 treatment months and had evaluable baseline and 12-month biopsies) was assessed for endometrial hyperplasia.

Overall, AEs of any kind were more common in the active treatment groups than with placebo. These AEs mostly consisted of headache, breast tenderness, nasopharyngitis, vaginal hemorrhage, vaginal discharge, abdominal pain, and dizziness. Most AEs were of mild-to-moderate severity. No cases of endometrial hyperplasia were observed during the trial in the 3 treatment groups over 12 months of follow-up, and there were 3 cases of breast cancer, all in the intervention groups, and none in the placebo group. The percentages of other AEs of special interest, such as VTE, superficial thromboses, cardiovascular events, cerebrovascular events, syncope, and malignancies, were low and did not occur with greater frequency in the intervention (1 mg/100 mg and 0.5 mg/100 mg) groups when compared to placebo.

Critical Appraisal

Prognostic variables were well balanced between the groups of the VMS substudy, with no major limitations in terms of the randomization process, allocation concealment, and outcome assessment. However, missingness of data was present due to analysis of end points as complete cases available, leading to possible imprecision of effect estimates and bias for the different end points. The magnitude and direction of this bias, however, are uncertain. The population included in the REPLENISH trial was considered generalizable to the Canadian landscape; however, certain patient groups (e.g., those at high-risk for cardiovascular disease or VTE) were not included and generalizability of the study results to these groups is uncertain. Furthermore, longer-term follow-up would be beneficial to assess the risk of outcomes (harms) such as cancer or cardiovascular events.

Economic Evidence

Cost and Cost-Effectiveness

At the submitted price of $0.90 per 0.5 mg/100 mg or 1 mg/100 mg capsule, the annual cost of the estradiol-progesterone capsules is $327 per patient. This annual cost is less than

that of its individual components when used daily ($568 to $608 per patient annually) or cyclically ($444 to $551 per patient annually). However, estradiol-progesterone capsules may displace other oral combination regimens, particularly in jurisdictions that do not reimburse progesterone. Estradiol-progesterone capsules are less expensive than combinations of conjugated estrogen and progesterone ($588 to $694 per patient annually) but more expensive than combinations of estradiol or conjugated estrogen plus medroxyprogesterone acetate ($74 to $202 per patient annually). Additionally, the use of estradiol-progesterone capsules would be associated with up to 12 fewer dispensing fees per year compared to combinations of estrogen and progesterone individual components. These incremental costs or savings are based on publicly available list prices and may not reflect actual prices paid by Canadian public drug plans.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the proportion of the population with VMS was overestimated; the population was not limited to those with an intact uterus; the proportion of the population eligible for public drug plan coverage was underestimated; comparator dosing was inappropriately estimated; transdermal estrogen products were assumed to be displaced; and the predicted uptake of estradiol-progesterone tablets is uncertain.

CADTH reanalysis included decreasing the proportion of people in menopause who experience VMS, removing patients without an intact uterus from the population of interest, increasing the proportion of public drug plan beneficiaries, altering assumptions around comparator dosing, and excluding transdermal estrogen products.

CADTH reanalyses reported that the reimbursement of estradiol-progesterone capsules for the treatment of moderate-to-severe VMS associated with menopause would be associated with a budgetary savings of $56,206 in year 1; $120,537 in year 2; and $181,588 in year 3; for a 3-year total incremental savings of $358,330, whereas the sponsor's estimated 3-year budget impact was cost savings of $756,083. Scenario analyses demonstrated that the savings in the CADTH reanalysis were largely due to savings in dispensing fees, as the 3-year budgetary impact when dispensing fees and markups were excluded was $177,273 in increased costs. The budgetary impact of estradiol-progesterone tablets is highly dependent on market uptake and displacement assumptions.

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: December 15, 2021

Regrets: Two expert committee members did not attend

Conflicts of interest: None