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CADTH Reimbursement Recommendation

Prasterone (Intrarosa)

Indication: For the treatment of postmenopausal vulvovaginal atrophy

Sponsor: Lupin Pharma Canada Ltd.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Intrarosa?

CADTH recommends that Intrarosa should be reimbursed by public drug plans for the treatment of postmenopausal vulvovaginal atrophy (VVA) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Intrarosa should only be covered for 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?

Intrarosa should only be reimbursed if treatment with Intrarosa does not cost more than treatment with the least costly vaginal estrogen product currently reimbursed for the treatment of postmenopausal VVA.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that Intrarosa improves the symptoms of painful sex and vaginal dryness, restores vaginal tissues, and improves vaginal pH levels better than placebo.
- Intrarosa provides a treatment option that is not a vaginal estrogen product for patients with postmenopausal VVA.
- Based on public list prices, Intrarosa costs more than most vaginal estrogen therapies. There is also no evidence to suggest it provides any benefit compared with other available treatment options.
- Based on public list prices, Intrarosa is expected to increase costs to the public drug plans by $14,019,986 over 3 years.

Additional Information

What Is Postmenopausal VVA?

Postmenopausal VVA is a condition in which the lining of the vagina thins due to the loss of estrogen after menopause. Approximately 60% to 90% of postmenopausal individuals may be affected by postmenopausal VVA. Symptoms include vaginal dryness, vaginal irritation, painful sex, and recurrent urinary tract infections.

Unmet Needs in Postmenopausal VVA

Patients may not respond to currently available treatments for postmenopausal VVA. Some patients may find the application of other vaginal estrogen therapies difficult, uncomfortable, or messy.

How Much Does Intrarosa Cost?

Treatment with Intrarosa is expected to cost approximately $532 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that prasterone be reimbursed for the treatment of postmenopausal vulvovaginal atrophy (VVA) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

There is evidence from 2 randomized, placebo-controlled trials that treatment with prasterone resulted in added clinical benefit for patients with postmenopausal VVA. Results from the ERC-238 (N = 554) and ERC-231 (N = 167, excluding irrelevant prasterone dosages) trials showed that treatment with prasterone 6.5 mg intravaginal ovule daily for 12 weeks was associated with statistically significant improvements compared with placebo in change from baseline to week 12 in severity of dyspareunia, severity of vaginal dryness, percentage of vaginal superficial cells, percentage of vaginal parabasal cells, and vaginal pH in patients with postmenopausal VVA with moderate to severe dyspareunia as the most bothersome symptom. The ERC-230 trial (N = 521), an open-label, single-group study, was supportive of maintained efficacy of prasterone for up to 52 weeks of treatment. Although efficacy was compared between prasterone and vaginal estrogen therapies in a published indirect treatment comparison, comparative efficacy was uncertain because of heterogeneity across the included trials and other limitations.

The clinical expert noted that some individuals with postmenopausal VVA have unmet needs because vaginal estrogen therapies have contraindications for certain patient populations (e.g., patients with breast cancer or a history of breast cancer, venous thromboembolism, or arterial thromboembolic disease) and serious warnings (some based on evidence from systemic estrogen replacement therapies) that can cause hesitancy in individuals for whom local estrogen therapies are appropriate. There is no evidence to support a safety benefit with prasterone over vaginal estrogen therapies; however, prasterone does not have the same contraindications and serious warnings that are associated with vaginal estrogen therapies.

Using the sponsor-submitted price for prasterone and publicly listed prices for all other drug costs, prasterone was more costly compared with most vaginal estrogen therapies. There was insufficient evidence to support a clinical benefit with prasterone versus relevant comparators. As such, there is no evidence to support a price premium with prasterone.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Reimburse in a similar manner as currently funded vaginal estrogen products.	No evidence was reviewed that supported a clinical benefit for prasterone compared with other therapies for postmenopausal VVA. At the time of this review, vaginal estrogen therapies were identified as the relevant comparators for prasterone.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
2. Prasterone should be negotiated so that its price does not exceed the least costly vaginal estrogen product reimbursed for the treatment of postmenopausal VVA.	There is insufficient evidence to justify a cost premium for prasterone over the least expensive vaginal estrogen product reimbursed for postmenopausal VVA.	—
Feasibility of adoption		
3. The feasibility of adoption of prasterone must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption because of the difference between the sponsor's estimate and CADTH's estimate.	—

VVA = vulvovaginal atrophy.

Discussion Points

- CDEC noted there is limited evidence available to support the efficacy and safety of prasterone in individuals with postmenopausal VVA who have contraindications (e.g., active or confirmed history of thromboembolism or estrogen-dependent cancer) to vaginal estrogen therapies.
- CDEC considered that there are limited data for long-term efficacy and safety of prasterone considering that postmenopausal VVA is a chronic condition. Notable harms, such as malignant neoplasm, are relatively rare events, and CDEC noted that longer follow-up is required to better understand the long-term safety of prasterone and whether it provides any safety benefit over vaginal estrogen therapies.
- CDEC considered that individuals with postmenopausal VVA who are currently not receiving vaginal estrogen therapies because of contraindications and/or serious warnings may opt for treatment with prasterone. In this situation, the market size of patients treated with therapies for postmenopausal VVA could increase with corresponding budget impact.

Background

Prasterone has a Health Canada indication for postmenopausal VVA. Prasterone is a synthetic form of dehydroepiandrosterone (DHEA), which is a natural steroid compound with no estrogenic, androgenic, or other hormonal activity. When prasterone is administered intravaginally, the cells in the vagina convert it into estrogen and androgens that act locally in the vaginal epithelium. The Health Canada recommended dosage is 1 ovule, which contains 6.5 mg prasterone, administered intravaginally once a day.

Sources of Information Used by the Committee

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

- a review of 3 clinical trials in patients with postmenopausal VAA
- a review of 1 published indirect treatment comparison
- a review of 3 additional studies in patients with postmenopausal VVA
- patients' perspectives gathered by 1 patient group: the Women's Health Coalition (WHC) of Alberta
- a summary prepared by CADTH of patients' experiences with menopause and libido, vaginal dryness, and urinary problems that were compiled from the website Healthtalk.org, a nonprofit 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 patients with postmenopausal VVA
- input from 2 clinician groups: Cleopatra and the Society of Obstetricians and Gynaecologists of Canada
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Input was received from 1 patient group, the WHC. The WHC advocates, raises awareness, and educates about urogynecological and reproductive health of patients 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 potential inequity in accessing preferred treatments that are not reimbursed by public drug plans. The WHC emphasized that clinical and psychological impacts caused by untreated menopausal-related conditions are often overlooked and dismissed and expressed the expectation that a positive reimbursement recommendation for prasterone would improve treatment options for postmenopausal individuals and potentially raise clinician awareness of the importance of treating menopausal-related 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 nonprofit organization that has collected hundreds of stories from patients with any health condition. Information from Healthtalk.org pertaining to VVA was obtained, assessed, and synthesized by the CADTH review team. This included video interviews with 13 British patients. The interviewed patients reported vaginal dryness, decline in libido, and urinary problems as some of the complications experienced after entering menopause. Most patients reported a decline in sexual activity due to loss of libido. Vaginal dryness was another issue patients reported encountering during menopause. Comments also acknowledged the importance of sex in a marriage and the important complications that can happen within a relationship over time due to decreased sexual activity and symptoms of VVA. During the interview, 1 woman was made aware of the 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 stated to cause severe discomfort for many of these patients, resulting in tears and bleeding. Patients also commented on their decreased estrogen which affects the pelvic floor, the bladder, the womb, the vagina, and bowel, leading to urinary and bowel problems. Comments about difficulty with incontinence and the impacts on quality of life were echoed by many other patients.

Clinician Input

Input From Clinical Experts Consulted by CADTH

One clinical specialist with expertise in the diagnosis and management of VVA provided input for this review.

The clinical expert consulting with CADTH for this review indicated that as many as 70% of postmenopausal individuals are expected to have genitourinary syndrome of menopause (GSM), a broader term which includes VVA, by the age of 70 years. GSM describes the consequences of hormone deficiency which affect urogenital tissues and result in genitourinary symptoms, compared with VVA, which focuses on changes in the genital tissues and related symptoms. Over-the-counter moisturizers and lubricants may provide patients with some symptomatic relief, but these treatments do not affect the underlying physiological changes associated with declining endogenous estrogen and can also be expensive for patients. Vaginal estrogen treatment was identified as the most effective treatment option for patients. However, all estrogen-based products (despite being systemic or local) have a black box warning issued from Health Canada for several disease risks, which limits its use for some patients. The clinical expert consulting with CADTH for this review stated that prasterone would provide patients with another treatment option because it can help improve their physiology and sexual function. In addition, prasterone could be an option for patients with contraindications for estrogen therapies, including patients with breast cancer or other estrogen-based cancers and patients with cardiovascular disease risk.

The dosing schedule of prasterone was acknowledged to be different than other estrogen-based therapies; other therapies are prescribed to patients at an interval of twice weekly, which some patients may easily forget, compared with prasterone which is administered daily. Patients who would benefit from treatment with prasterone would be identified by an experienced clinician both by a physical examination and by asking patients about symptoms of GSM and sexual function. According to the clinical expert, a patient's response to treatment can be assessed through self-reported symptoms and a clinical examination of vaginal colour, lubrication, sensation, and pain. Any reduction of GSM symptoms (e.g., dyspareunia, dryness, pain, discomfort, burning, itch, dysuria) was stated to be considered a clinically meaningful response to treatment. Response to treatment was stated by the expert to be assessed 3 months to 4 months after treatment initiation, although some studies suggest that patients may improve dramatically within the first month of treatment. After an initial assessment of treatment, it may not be necessary to continue assessing patient's response to treatment unless a new symptom occurs or symptoms worsen. Adverse events (AEs) were not considered a concern because the clinical expert believed that prasterone is a very well-tolerated treatment. The clinical expert confirmed that prasterone may be prescribed by family physicians or at specialty clinics, including gynecology, urology, or urogynecology clinics. Diagnosis of postmenopausal VVA can be made by a family physician, nurse practitioner, or a specialist if referred to one (i.e., gynecologist, urologist).

Clinician Group Input

Input was received from 2 clinician groups: Cleopatra (prepared by 2 registered nurses) and the Society of Obstetricians and Gynaecologists of Canada (prepared by 1 physician). No major contrary views were presented. Both clinician groups highlighted that many individuals may suffer from VVA and that prasterone may provide a useful treatment option to treat symptoms and the underlying condition.

Drug Program Input

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The sponsor's studies have only compared prasterone to placebo. Vagifem is a possible comparator and is covered in most provinces. Vagifem is a low-dose, twice-weekly estrogen insert that was not directly compared with prasterone in the submitted trials.	CDEC agreed with the drug programs that there is limited evidence available comparing prasterone to active comparators. CDEC noted that therapy selection may be based on application acceptability, patient preference, and whether there is hesitancy about using estrogen-based products. However, there is inadequate information available to guide the selection of prasterone over Vagifem or other vaginal estrogen products.
Considerations for initiation of therapy	
The studies included patients with moderate to severe VVA. There is uncertainty about whether severity matters and if it can be measured.	The clinical expert commented that severity can be measured using a Likert scale or by using subscales from the FSFI. In clinical practice severity of symptoms may be assessed by determining the impacts of symptoms on patients. For example, patients who experience dyspareunia to the point of being unable to engage in sexual activity may be considered to have moderate to severe dyspareunia. CDEC did not have any further comments to add.
Moisturizers and lubricants should remain first-line treatments, after which prasterone and low-dose estrogen topicals and inserts are possible options. This medication was not directly compared to Vagifem; therefore, there is no evidence to say one is more efficacious than the other. Would a patient need to say one prefers a non-estrogen therapy to receive this? Or are there other factors such as cancer treatment that would necessitate non-estrogen therapy?	The clinical expert commented that some patients are hesitant to try estrogen therapies due to fears related to increased risk of cancers, blood clots, and/or stroke. Despite education about the low risk to patients, patients remain hesitant to try these therapies. Prasterone would be a useful treatment option for patients who would prefer not to take, or are contraindicated for treatment with, estrogen-based therapies. However, such reasons are not necessary to prescribe prasterone, and it is appropriate to consider prasterone as a first-line treatment option for patients seeking medical care. In general, patient preference should be considered when prescribing therapies for postmenopausal individuals with VVA. CDEC agreed with the clinical expert's input.

Implementation issues	Response
Considerations for prescribing of therapy	
If used with other topical or vaginal insert treatments or with other hormonal therapies, there is potential for androgen and estrogen levels to rise with this medication. With additional treatments, this could be exponential.	The clinical expert stated that use of 2 local therapies would not be recommended. Use of prasterone may impact circulating androgen levels; the clinical expert commented that levels would not be increased to significant levels which warrant concern. Prasterone may be used in combination with testosterone therapy. Clinical guidelines for testosterone treatment recommend that androgen levels be assessed every 6 months. Therefore, any additive effects of treatments used in combination with prasterone would likely be observed during a patient's assessment. CDEC did not have any further comments to add.

CDEC = CADTH Canadian Drug Expert Committee; FSFI = Female Sexual Function Index; VVA = vulvovaginal atrophy.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

A total of 3 studies were summarized and critically appraised in this CADTH report: the ERC-238, ERC-231, and ERC-230 trials. The ERC-238 trial was a phase III, double-blind, placebo-controlled, multicentre trial to compare the efficacy of 12 weeks of treatment with a once-daily intravaginal prasterone ovule at 0.5% (N = 374) compared with a once-daily intravaginal placebo ovule (N = 180) on pain at sexual activity (dyspareunia) in postmenopausal individuals aged 40 years to 80 years with dyspareunia as their most bothersome symptom of VVA. The ERC-231 trial was a phase III, double-blind, placebo-controlled, multicentre trial that assessed the efficacy of intravaginal prasterone at 6.5 mg (N = 87) or 3.25 mg compared with placebo (N = 80) in postmenopausal individuals with moderate to severe dyspareunia as their most bothersome symptom of VVA at baseline. Only the prasterone 0.5% (6.5 mg) group was considered relevant for this CADTH review because this is the dose approved by Health Canada. The results for the prasterone group that are presented for the ERC-231 trial are those from the prasterone 0.5% group alone. The duration of the trial was 12 weeks. The ERC-230 trial was a phase III, open-label, single-group study (N = 521) that examined the long-term safety of daily treatment with intravaginal prasterone (6.5 mg). The trial duration was 52 weeks.

The 4 co-primary end points of the ERC-238 and ERC-231 trials included percentage of parabasal cells, percentage of superficial cells, vaginal pH, and severity of dyspareunia score. Secondary end points included sexual function (measured using the Female Sexual Function Index [FSFI]), vaginal dryness, vaginal irritation and/or itching, and safety. The primary objective of the ERC-230 trial was to evaluate the long-term safety of prasterone in postmenopausal individuals with VVA; safety was assessed through AEs, mammography, Papanicolaou (Pap) test, endometrial biopsy, and other outcomes. Secondary end points of the ERC-230 trial included percentage of parabasal cells, percentage of superficial cells, vaginal pH, severity score of dyspareunia, sexual function (measured using the FSFI), vaginal dryness, and vaginal irritation and/or itching.

Baseline characteristics were similar in the prasterone and placebo groups in the ERC-238 and ERC-231 trials as well as between the 2 trials. In all 3 trials, the median age of participants was between 57 years and 59 years and most (> 85%) were White and non-Hispanic or non-Latino (≥ 88%). Patients reported both natural and surgical causes of their last menstruation, which occurred at mean ages between 44 years and 50 years. Previous hormone therapy was reported by approximately half of patients in all trials. Key differences between trials included mean years since last menstruation (13 years to 14 years for patients in the ERC-238 and ERC-231 trials versus approximately 8 years in the ERC-230 trial), proportion of patients reporting a hysterectomy (39% in the ERC-238 trial versus 60% in the ERC-231 trial; patients in ERC-230 were not hysterectomized), and oophorectomy (27% to 30% in the ERC-238 and ERC-231 trials, respectively, compared with 5% in the ERC-230 trial).

Efficacy Results

A summary of the 4 co-primary end points of the ERC-238 and ERC-231 trials and the secondary end point of vaginal dryness are summarized here, along with the corresponding results for the ERC-230 trial. The efficacy analyses presented for the ERC-238 and ERC-231 trials were performed in the intention-to-treat population; per-protocol analysis results were similar to these results.

Dyspareunia

In the ERC-238 trial, the mean change from baseline in severity of dyspareunia score was greater for the prasterone group (mean change = −1.42; standard deviation [SD] = 1.00) compared with the placebo group (mean change = −1.06; SD = 1.02) at 12 weeks; the mean difference for the prasterone group versus the placebo group was −0.35 (SD = not reported [NR]; P = 0.0002) in favour of prasterone. In the ERC-231 trial, the mean change from baseline in severity of dyspareunia score was greater for the prasterone group (mean change = −1.27; SD = 0.99) compared with the placebo group (mean change = −0.87; SD = 0.95) at 12 weeks; the mean difference for the prasterone group versus the placebo group was −0.40 (SD = NR; P = 0.0132) in favour of prasterone. In the ERC-230 trial, the mean severity of dyspareunia score was reported for patients who had moderate to severe dyspareunia as their most bothersome symptom at baseline and met VVA criteria for superficial cells (≤ 5%) and vaginal pH (> 5.0) (n = 183). The severity of dyspareunia score was 2.57 (SD = 0.50) at baseline and 0.87 (SD = 0.96) at week 52; the mean change from baseline was −1.69 (SD = 0.97). The mean severity of dyspareunia score was also reported for patients who had moderate to severe dyspareunia at baseline and met VVA criteria for superficial cells (≤ 5%) and vaginal pH (> 5.0) (n = 240). The severity of dyspareunia score was 2.53 (SD = 0.50) at baseline and 0.85 (SD = 0.95) at week 52; the mean change from baseline was −1.68 (SD = 0.95).

Vaginal Dryness

Both the ERC-238 and ERC-231 trials demonstrated statistically significant improvement with prasterone in symptom score for dyspareunia and statistical testing for vaginal dryness score was conducted in patients with moderate to severe vaginal dryness at baseline. In the ERC-238 trial, the mean change from baseline in severity of vaginal dryness score was greater for the prasterone group (mean change = −1.44; SD = 0.93) compared with the placebo group (mean change = −1.17; SD = 0.99) at 12 weeks; the mean difference for prasterone versus placebo was −0.27 (SD = NR; P = 0.004). In the ERC-231 trial, the mean change from baseline in severity of vaginal dryness score was similar for the prasterone group (mean change = −1.45; SD = 0.95) compared with the placebo group (mean change = −1.02; SD = 1.08) at 12 weeks; the mean difference for prasterone versus placebo was −0.43 (SD = NR; P = 0.0128). In the ERC-230 trial, the severity of vaginal dryness score was also reported for patients

who reported moderate to severe vaginal dryness at baseline and met VVA criteria for superficial cells (≤ 5%) and vaginal pH (> 5.0) and who reported vaginal dryness as their most bothersome symptom (n = 81). The mean severity of vaginal dryness score was 2.19 (SD = 0.39) at baseline and 0.67 (SD = 0.81) at week 52; the mean change from baseline was −1.52 (SD = 0.78). The mean severity of vaginal dryness score for patients who reported moderate to severe vaginal dryness at baseline (n = 251) was 2.22 (SD = 0.42) at baseline and 0.59 (SD = 0.74) at week 52; the mean change from baseline was −1.63 (SD = 0.79).

Vaginal Cell Maturation

Vaginal cell maturation was assessed using the change from baseline of the percentages of parabasal and superficial cells. In the ERC-238 trial, the mean change from baseline in the percentage of parabasal cells was greater for the prasterone group (mean change = −41.51%; SD = 36.26%) compared with the placebo group (mean change = −11.98%; SD = 29.58%) at 12 weeks; the mean difference for the prasterone group versus the placebo group was −29.53% (SD = NR; P < 0.001) in favour of prasterone. In the ERC-231 trial, the mean change from baseline in the percentage of parabasal cells was greater for the prasterone group (mean change = −47.40%; SD = 42.50%) compared with the placebo group (−1.62%; SD = 28.22%) at 12 weeks; the mean difference for the prasterone group versus the placebo group was −45.77% (SD = NR; P < 0.0001) in favour of prasterone. In the ERC-230 trial, the mean change from baseline to week 52 in percentage of parabasal cells for all patients treated with prasterone was −42.67% (SD = 39.23%). The mean change in percentage of parabasal cells was also analyzed in a group of 292 patients who had dyspareunia, vaginal dryness, or vaginal irritation and/or itching as their most bothersome symptom. The mean change from baseline to week 52 in percentage of parabasal cells for all patients treated with prasterone in this group was −49.14% (SD = 37.91%).

The mean change from baseline in the percentage of superficial cells was greater for the prasterone group (mean change = 10.20%; SD = 10.35%) compared with the placebo group (mean change = 1.75%; SD = 3.33%) at 12 weeks in the ERC-238 trial; the mean difference for the prasterone group versus the placebo group was 8.46% (SD f= NR; P < 0.001) in favour of prasterone. In the ERC-231 trial, the mean change from baseline in the percentage of superficial cells was greater for the prasterone group (mean change = 5.62%; SD = 5.49%) compared with the placebo group (mean change = 0.91%; SD = 2.69%) at 12 weeks; the mean difference for the prasterone group versus the placebo group was 4.71% (SD = NR; P < 0.0001) in favour of prasterone. In the ERC-230 trial, the mean change from baseline to week 52 in percentage of superficial cells for all patients treated with prasterone was 7.41% (SD = 8.06%). The mean change in percentage of superficial cells were also analyzed in a group of 292 patients who had dyspareunia, vaginal dryness, or irritation and/or itching as their most bothersome symptom. The mean change from baseline of superficial cells for all patients treated with prasterone in this group was 7.85% (SD = 7.15%).

Vaginal pH

In the ERC-238 trial, the mean change from baseline in vaginal pH was greater for the prasterone group (mean = −0.94; SD = 0.94) compared with the placebo group (mean change = −0.27; SD = 0.74) at 12 weeks; the mean difference for prasterone versus placebo was −0.67 (SD = NR; P < 0.0001) in favour of prasterone. In the ERC-231 trial, the mean change from baseline in vaginal pH was greater for the prasterone group (mean change = −1.04; SD = 1.00) compared with the placebo group (mean change = −0.21; SD = 0.69) at 12 weeks; the mean difference for prasterone versus placebo was −0.83 (SD = NR; P < 0.0001) in favour of prasterone. In the ERC-230 trial, the mean change from baseline to week 52 in vaginal pH

for all patients treated with prasterone was −1.14 (SD = 0.96). The mean change in vaginal pH was also analyzed in a group of 293 patients who had dyspareunia, vaginal dryness, or irritation and/or itching as their most bothersome symptom. The mean change from baseline to week 52 of vaginal pH for all patients treated with prasterone in this subgroup was −1.27 (SD = 0.90).

Harms Results

Adverse Events

The proportion of patients reporting at least 1 AE in the ERC-238 trial was similar in both treatment groups: 179 patients (47.9%) in the prasterone group and 77 patients (42.8%) in the placebo group. In the ERC-231 trial, there was a higher proportion of patients with at least 1 AE in the prasterone group than the placebo group: 46 (52.9%) patients in the prasterone group and 35 (43.8%) patients in the placebo group. A greater proportion of AEs were reported in the ERC-230 trial, with 418 patients (80.2%) experiencing AEs. The most commonly reported AEs across all trials were application site discharge (ERC-238: 6.1% in the prasterone group versus 5.6% in the placebo group; ERC-231: 5.7% versus 6.3%, respectively; ERC-230: 14.0% in the prasterone group) and urinary tract infections (4.5% in the prasterone group versus 2.8% in the placebo group; ERC-231: 5.7% versus 5.0%, respectively; ERC-230: 10.2% in the prasterone group).

Serious Adverse Events

Serious AEs (SAEs) were rare in all trials. In the ERC-238 trial, 6 (1.6%) patients in the prasterone group experienced an SAE compared with zero patients in the placebo group. In the ERC-231 trial, 1 (1.1%) patient in the prasterone group experienced an SAE compared with zero patients in the placebo group. In the ERC-230 trial, SAEs occurred in 18 (3.5%) patients.

Discontinuations Due to Adverse Events

Few patients discontinued treatment due to an AE in any of the trials, and reporting of AEs was generally consistent for all treatment groups. In the ERC-238 trial, 5 (1.3%) patients in the prasterone group versus 5 (2.8%) patients in the placebo group discontinued treatment due to an AE. In the ERC-231 trial, 2 (2.3%) patients in the prasterone group and 1 (1.3%) patient in the placebo group discontinued treatment due to an AE. In the ERC-230 trial, 31 (6.0%) patients discontinued treatment due to an AE.

Mortality

There were no deaths in any of the trials.

Notable Harms

Notable harms identified in the CADTH systematic review protocol included vaginal hemorrhage, endometrial dysplasia, cervical dysplasia, and breast mass. Few patients experienced notable harms reported as AEs in the ERC-238, ERC-231, and ERC-230 trials, and there was little to no difference in reporting of notable harms across treatment groups. Vaginal hemorrhage was reported in 1.1% of patients in both the prasterone and placebo groups in the ERC-238 trial; zero patients and 2.5% of patients in the prasterone and placebo groups, respectively, in the ERC-231 trial; and 2.5% of patients in the ERC-230 trial. Cervical dysplasia was reported in 1.9% of patients in the prasterone group versus zero patients in the placebo group in the ERC-238 trial, 3.4% of patients in the prasterone group versus 2.5% of patients in the placebo group in the ERC-231 trial, and 3.8% of patients in the ERC-230 trial. Breast mass was reported in 0.3% of patients in the prasterone group versus zero patients in

the placebo group of the ERC-238 trial, 0.4% of patients in the ERC-230 trial, and zero patients in the ERC-231 trial.

The ERC-230 trial also reported on breast, endometrial, and cervical safety. Endometrial safety was also reported in the ERC-231 trial. Breast examinations were conducted at screening and at week 52 and mammograms were performed prior to day 1 and at week 52. A total of 451 patients (98%) had a mammogram; 455 patients (99%) showed normal or no significant findings based on breast examination and/or mammogram. Significant breast pathology was observed in 2 participants, which included 1 case each of atypical ductal hyperplasia and infiltrating carcinoma. Undetermined status was reported in 2 patients, 1 patient refused follow-up, and the findings from the other patient were reported as being probably benign. The results of the remaining 15 patients were reported to be benign. In general, normal breast findings were observed in patients who received long-term treatment with prasterone and long-term administration of prasterone in the ERC-230 trial was not associated with cervical dysplasia. Pap tests were conducted for patients who received prasterone for at least 26 weeks. A Pap test was conducted for 430 of 432 patients who received prasterone for 52 weeks (90%). A total of 13 patients yielded results of atypical squamous cells of uncertain significance, low-grade squamous intraepithelial lesion, or high-grade squamous intraepithelial lesion. Of these 13 patients, 7 had a negative human papillomavirus (HPV) test or colposcopy. In the ERC-231 trial, approximately 40% of patients were not hysterectomized and underwent an endometrial biopsy at screening (25 to 31 patients per treatment group). Almost all the patients who were not hysterectomized (99%), including 28 patients in the prasterone group and 27 patients in the placebo group, underwent an endometrial biopsy at week 12; 5 patients in the prasterone group and 2 patients in the placebo group did not have sufficient tissue for biopsy at this time. At week 12, the endometrium of all evaluable patients was atrophic, and the sponsor reported no clinically significant results. In the ERC-230 trial, endometrial biopsies were performed for patients who received prasterone for at least 3 months. For patients with unevaluable endometrial biopsies or who refused endometrial biopsies at the end of treatment, transvaginal ultrasounds were performed (43 patients). In total, 457 patients (94%) had a biopsy at the end of the 52-week study period. For patients who underwent a biopsy, the endometrium of most patients (91%) was atrophic. For the 43 patients who underwent a transvaginal ultrasound, the average endometrial thickness was 2.2 (SD = 1.4) mm. There were no clinically significant histological findings in the ERC-230 trial with long-term use of prasterone.

Indirect Comparisons

Description of Studies

The CADTH literature search identified 1 network meta-analysis (NMA) by Li et al. in which several NMAs were conducted to indirectly compare treatment with prasterone to other treatments for VVA in patients with menopause. A total of 29 trials incorporating a total of 8,311 patients were included in the indirect treatment comparison by Li et al. and evaluated the following treatments: laser therapy, vaginal estrogen, ospemifene, vaginal DHEA (i.e., prasterone), and moisturization and/or lubrication.

The NMA included both open-label and blinded randomized controlled trials that were published between 1992 and 2020. All patients included in the trials were between 50 years and 62 years of age. All trials except 4 excluded patients with breast or gynecological cancers. Treatment duration was heterogeneous, with most trials assessing treatment for 12 weeks. Outcomes assessed included urinary and sexual outcomes (i.e., dryness, itching, dyspareunia,

urinary tract infections), AEs, and health-related quality of life assessed through various tools. Different doses of treatments were also used in the 29 trials; for DHEA, studies assessing doses of 0.5% (6.5 mg) and 0.25% (2.25 mg) were included. The authors did not report on the number of studies included for the NMAs of any end points assessed (vaginal dryness, vaginal burning and itching, dyspareunia, sexual function, vaginal pH, proportion of parabasal cells, and AEs) nor on their risk of bias. It is not clear how the nodes were created, although it appears that similar treatments were merged regardless of dose and duration. The tool used to measure the end points across the included trials was not specified. The network structure was not described. The authors indicated that the model converged "adequately" but relevant data were not provided to support this assertion.

Efficacy Results

Vaginal Dryness

No differences were observed between DHEA and vaginal estrogen therapy for vaginal dryness (mean difference = 0.32; 95% credible interval [CrI], −8.54 to 8.77). The I^2 value for heterogeneity was 0%, but the pairwise frequentist analyses showed high heterogeneity. Subgroup analyses did not seem to explain the heterogeneity for the comparisons of interest (DHEA versus other treatments). There did not appear to be any sensitivity analyses performed for this comparison. Publication bias was not detected.

Dyspareunia

Little to no difference was observed between DHEA and vaginal estrogen therapy for dyspareunia (mean difference = −4; 95% CrI, −14 to 4). The I^2 value for heterogeneity was 11%.

Sexual Function

No differences were observed between DHEA and vaginal estrogen therapy for sexual function as measured by the FSFI (mean difference = 1.04; 95% CrI, −1.99 to 3.93). The I^2 value for heterogeneity was 0%.

Vaginal pH

The I^2 value for heterogeneity for vaginal pH was 4%. Vaginal estrogen therapy (mean difference = 0.4; 95% CrI, 0.1 to 0.7) was favoured over DHEA.

Proportion of Parabasal Cells

No differences were observed between DHEA and vaginal estrogen therapy for proportion of parabasal cells (mean difference = 1.6%; 95% CrI, −12.5% to 13.8%). The I^2 value for heterogeneity was 9%.

Harms Results

No difference was found between DHEA and vaginal estrogen therapy for risk of AEs (odds ratio = 1.54; 95% CrI, 0.91 to 2.62). The I^2 value for heterogeneity was less than 25% among treatments.

Critical Appraisal

Although several databases were searched for the systematic review, the authors did not search other sources (e.g., clinical trial registries) so it is possible that some relevant studies were missed. Methods of data extraction were not described, so error within the findings is possible. Studies were assessed for risk of bias, but it is not clear how this assessment was carried out, so it is difficult to assess the validity of these assessments. Differences in trial

and baseline characteristics are likely to have impacted the indirect comparisons, although the exact effect of these difference is unclear. An assessment of similarity across trials in each NMA was not conducted; therefore, whether underlying assumptions of the NMAs (i.e., homogeneity and transitivity) have been met are uncertain. There was a lack of clear reporting regarding the construction of nodes in the NMAs. However, based on reported information it was assumed that treatment doses, durations, and outcomes measures for single treatments were combined into single nodes. The combination of different doses, durations, and outcomes measures for treatments is likely to have introduced bias because the efficacy and safety of treatments that may not have been administered or measured the same is uncertain. Credible intervals were also wide, which indicates the potential for substantial uncertainty between treatment comparisons, including the comparisons between DHEA and vaginal estrogen therapies. Subgroup and sensitivity analyses revealed sources of variation for each end point. It is probable that heterogeneity across trials affects the confidence of results of the NMA.

Other Relevant Evidence

The following studies were included as additional evidence: the ERC-210 trial, the Estip-Es study, and a Barton et al. study. The ERC-210 trial was a phase III, double-blind, multicentre, randomized, placebo-controlled trial to determine the dose-response of prasterone on symptoms and vaginal mucosa parameters in postmenopausal individuals with VVA. The Estip-Es study was an observational study conducted in Spain that evaluated the effectiveness and safety of prasterone in a real-world clinical setting. The study by Barton et al. examined the use of prasterone for treatment of postmenopausal VVA symptoms in individuals with a history of breast or gynecological cancer.

Description of Studies

The ERC-210 trial, which began in June 2007 and completed in October 2008, was a multicentre (US and Canada), prospective, double-blind, randomized, parallel-assignment, placebo-controlled, phase III trial to determine the dose-response of prasterone on symptoms and vaginal mucosa parameters in postmenopausal individuals with VVA. The study informed the dose of prasterone to use for the subsequent phase III studies. Patients were randomized to receive prasterone at 3.25 mg (n = 53), 6.5 mg (n = 56), or 13.0 mg (n = 54) or placebo (n = 53). Only the 6.5 mg dose of prasterone was relevant to this review.

The Estip-Es study was a multicentre, prospective, noncomparative, observational study with 184 adult postmenopausal individuals who were routinely seen in medical centres throughout Spain for GSM. Patients had used vaginal moisturizers or lubricants and/or vaginal hormone therapy and switched to intravaginal prasterone without a washout period.

The study by Barton et al. was a multicentre (US and Canada), 3-group, double-blind, parallel-group, randomized controlled trial in which 443 patients were randomized to receive either 3.25 mg (n = 147) or 6.5 mg of prasterone (n = 149) in a plain bioadhesive moisturizer or a plain bioadhesive moisturizer alone (n = 147). Only the 6.5 mg dose of prasterone was relevant to this review.

Efficacy Results

ERC-210 Study

The percentage of superficial cells was measured to be 0.62% (SD = 1.02%) at baseline and 0.54% (SD = 0.95%) at week 12 in the placebo group. The percentage of superficial cells was

measured to be 0.40% (SD = 0.62%) at baseline and 5.20% (SD = 6.54%) at week 12 for the prasterone group. The mean difference in change in percentage of superficial cells between the prasterone group and the placebo group at week 12 was 4.88% (P = 0.0111) .

The percentage of parabasal cells was measured to be 46.73% (SD = 44.05%) at baseline and 47.81% (SD = 38.36%) at week 12 for the placebo group. The percentage of parabasal cells was measured to be 53.40% (SD = 41.01%) at baseline and 11.00% (SD = 18.77%) at week 12 for the prasterone group. The mean difference in change in percentage of parabasal cells between the prasterone group and the placebo group at week 12 was 43.48% (P < 0.0001).

In the placebo group, mean vaginal pH was 6.49 (SD = 0.69) at baseline and 6.01 (SD = 1.12) at week 12. In the prasterone group, mean vaginal pH was 6.64 (SD = 0.51) at baseline and 5.17 (SD = 0.91) at week 12. At week 12, there was a mean difference in change in vaginal pH of −0.99 (P = 0.0001) in the prasterone group compared with the placebo group.

The mean severity of dyspareunia score was 2.77 (SD = 0.43) at baseline and 2.35 (SD = 0.94) at week 12 (P = 0.0132) for the placebo group. In the prasterone group, the mean severity of dyspareunia score was 2.73 (SD = 0.45) at baseline and 1.10 (SD = 1.18) at week 12. There was a mean difference in change in severity of dyspareunia score of −1.21 (P < 0.0001) in the prasterone group compared with the placebo group at week 12.

Estip-Es Study

In the overall study population, the total FSFI score increased from 15.7 (SD = 6.3) to 19.9 (SD = 5.38), with a mean change of 4.2 over 30 days. Scores increased from baseline to posttreatment with prasterone in all the FSFI domains with variable magnitudes. A visual analogue scale to assess the self-reported impact on GSM across 19 items encompassed symptoms including dryness, dyspareunia, bleeding, burning, itching, urinary problems and infections, and abdominal pain. Visual analogue scale scores decreased (showing improvement) for all symptoms except for vaginal discharge; however, application site discharge is an expected AE related to use of prasterone.

Barton et al. Study

The primary end point in the Barton et al. study was self-rated severity of patients' most bothersome symptom, either dryness or dyspareunia, using an ordinal scale of none, mild, moderate, severe, or very severe. There was no difference between the 6.5 mg prasterone group (mean = −1.8; 95% CI, −1.97 to −1.54) and the plain moisturizer group (mean = −1.5, 95% CI, −1.74 to −1.27; P = 0.08) in changes in the severity of the most bothersome symptom (dryness or dyspareunia) at week 12.

Harms Results

ERC-210 Study

Of patients who received prasterone in the ERC-210 study, 47 (84%) experienced at least 1 AE compared with 35 (65%) in the placebo group. The most common AEs (≥ 5%) reported in prasterone group were cough (11%), headache (9%), and vaginal discharge (9%). The percentage of patients who withdrew from treatment due to an AE was 4% for both the placebo and prasterone groups. For the prasterone group, 1 (2%) patient had cervical dysplasia; none had vaginal hemorrhage.

Estip-Es Study

In the overall population of the Estip-Es study, 6.5% of patients reported AEs (e.g., blisters on the face, hair loss, constipation, leukorrhea, and dizziness) at follow-up at 30 ± 7 days. No further details regarding these AEs were provided in the published article.

Barton et al. Study

The most common clinician-graded AEs (reported in > 5% of any treatment group) included headache and breast pain, the incidence of which did not differ between treatment groups.

Critical Appraisal

ERC-210 Study

The plan for the primary analysis in the ERC-210 study was amended following feedback from the FDA to restrict to the subgroup of patients who identified dyspareunia as their most bothersome symptom at baseline. This revision was post hoc and in a subgroup of patients, thereby breaking randomization. The direction and extent of any selection bias related to imbalances in characteristics is unclear because updated baseline characteristics for the subgroup were not reported. However, the Bonferroni adjustment for the co-primary analyses was a conservative approach to help mitigate the potential bias introduced by the revised analysis. The differences between the prasterone 0.5% and placebo groups were statistically significant following the Bonferroni adjustment. The sample sizes of patients randomized to the prasterone and placebo groups were 56 and 54, respectively. The amendment of the analysis to a subgroup of these patients meant that the sample sizes were reduced to 30 patients and 26 patients in the prasterone and placebo groups, respectively, with no information regarding baseline characteristics of this subgroup population provided. Because moisturizer (placebo) may have some effect on vaginal parameters and symptoms, the treatment effect of the prasterone ovule may have been smaller versus the placebo ovule than it would have been versus a true placebo. The relatively short follow-up and small number of patients in the ERC-210 study are inadequate to confirm long-term benefits of prasterone beyond 12 weeks and assess rare, long-term harms.

Estip-Es Study

The Estip-Es study was an observational study with the objective of evaluating the efficacy, safety, and tolerability of prasterone for the treatment of postmenopausal individuals with GSM in clinical practice. Because there was no comparator group, the efficacy of prasterone relative to other therapies was not clear based on data from this study. In addition, the nature of this study design could have introduced bias due to confounding patient characteristics that could not be controlled for. The lack of blinding to treatment allocation and the subjective nature of all the outcomes could have contributed to patients reporting greater improvements with a switch to prasterone than they would have in a double-blind randomized controlled trial. Patients enrolled in the Estip-Es study were not subject to a washout period; therefore, it is possible that residual effects from previous treatments may have carried over and affected patient outcomes while receiving treatment with prasterone. The study used a "validated short version with 7 items" for FSFI; however, no references were provided related to the validity and reliability of the short form. Due to the lack of detailed information on patient's baseline characteristics, it is difficult to ascertain to what extent the enrolled population reflects the Canadian population who are eligible for treatment with prasterone. The small sample size further limits generalizability of this study to the Canadian population. The Estip-Es study enrolled individuals from medical centres throughout Spain for GSM; therefore, these individuals were seeking medical intervention for symptoms related to VVA. Due to this, there

is a possibility of selection bias because patients who were dissatisfied with their previous treatments were likely to have been enrolled in the Estip-Es trial and may have viewed treatment with prasterone more positively. Follow-up visits for patients were conducted approximately 1 month after recruitment into the Estip-Es study. This short-term follow-up may not be an optimal time frame to capture benefits and harms related to treatment with prasterone.

Barton et al. Study

The Barton et al. study was conducted for 12 weeks, which may not have been an ideal duration for capturing the efficacy and safety of treatment with prasterone in postmenopausal individuals with a history of breast and gynecological cancers. Treatment with prasterone may occur for long periods of time, and longer-term data would be necessary for understanding the long-term impact of treatment in this patient population with a history of hormone-dependent cancers. For the primary outcome, approximately 20% and 25% patients discontinued before completion of study in the plain moisturizer and 6.5 mg prasterone groups, respectively. Primary analysis was based on a completed analysis set ("primary end point" data) and was not done in an intention-to-treat method. Therefore, the high rate of study discontinuations (missing data of ≥ 20% in each group) introduces uncertainty in the results, and it is unclear how the last value carried forward missing data imputation method may have biased the results. Also, it is unclear if the last observation carried forward missing data imputation method was used for all the other analyses besides primary outcomes (i.e., FSFI and quality of life). After all the losses to follow-up, the primary end point dataset did not meet their intended sample size (i.e., 145 patients in each arm), so the study is at risk of being underpowered. This study specified that patients administer compounded intravaginal prasterone in a gel formulation using a syringe (without a needle), whereas the Health Canada product monograph specifies that prasterone be administered as an ovule and inserted using an applicator. Therefore, comparability with other studies that assess prasterone as an ovule versus the gel is limited.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Postmenopausal patients with VVA who exhibited moderate to severe dyspareunia as their most bothersome symptom
Treatment	Prasterone
Submitted price	6.5 mg, $1.46 per ovule ($40.78 per box of 28 ovules)
Treatment cost	$532 per patient per year

Component	Description
Comparators	• Estradiol vaginal tablet (10 mcg) and no treatment in base case • CE cream, estrone cream, and estradiol ring included in scenario analysis
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	30 years
Key data source	ERC-231 and ERC-238 clinical trials for prasterone and no treatment, studies from the literature informed key data for CE cream, estrone cream, and estradiol ring.
Submitted results	• Base case: ICER = $9,861 per QALY ($378 incremental costs, 0.04 incremental QALYs) compared to no treatment. Estradiol vaginal tablets were dominated by prasterone. • Scenario analysis with additional cream and ring local hormone therapies: All comparators dominated by CE cream (i.e., CE cream associated with fewer costs and greater QALYs).
Key limitations	• Local hormone therapies used in clinical practice to treat dyspareunia were excluded from the sponsor's base case. These were deemed to be relevant comparators in determining the cost-effectiveness of prasterone. • No comparative data between prasterone and active comparators was available, making the comparative efficacy and safety of prasterone with relevant comparators beyond no treatment highly uncertain. The sponsor incorporated treatment effects in the model via a naive comparison. As a result, model predications related to treatment response and discontinuation are highly uncertain. • Treatment for VVA is often iterative, and patients may discontinue and restart the same product or switch to other products over time. The submitted model does not allow for subsequent therapies to be used nor does it account for the iterative nature of VVA treatment. • Discontinuation rates were highly uncertain and may be overestimated due to the reliance on trial withdrawal rates to estimate long-term treatment discontinuation rates. The trial rates informing the model may have overestimated the likelihood of long-term discontinuation. • The dosing of estradiol vaginal tablets and CE cream was overestimated, therefore overestimating drug costs associated with these treatments.
CADTH reanalysis results	• Due to the extent of uncertainty with the clinical evidence in the model, a CADTH base case could not be derived. • In an exploratory reanalysis, CADTH included all relevant comparators, response and discontinuation rates were assumed equal for all active comparators, and the dosing of estradiol tablets and CE cream were adjusted to reflect their use in clinical practice. • Based on CADTH reanalyses, prasterone was dominated by CE cream given prasterone was more costly than CE cream while being equally effective. A price reduction of 89% would be required for prasterone to be considered cost-effective. • Uncertainty remains due to the lack of available comparative clinical effectiveness and safety data.

CE = conjugated estrogen; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; VVA = vulvovaginal atrophy.

Budget Impact

CADTH identified several key limitations with the sponsor's analysis, which included an assumption that prasterone would only displace estradiol vaginal tablets, the availability of prasterone expanding the total number of claims for VVA therapies beyond those of the current comparators as estimated by the sponsor, uncertainty with the market uptake of prasterone, and the overestimation of dispensing fees for comparators.

CADTH reanalyses included assuming all available comparators used to treat VVA in Canada will be displaced, assuming the availability of a non–estrogen-based treatment options will increase the market size of available VVA therapies, and reducing the number of dispensing fees applied to available comparators.

Based on CADTH reanalyses, the budget impact of reimbursing prasterone for patients with postmenopausal VVA is expected to be $2,272,680 in year 1, $4,641,494 in year 2, and $7,105,812 year 3, for a 3-year budget impact of $14,019,986. This estimate was substantially different from that of the sponsor (3-year total: a savings of $453,447).

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: February 24, 2022

Regrets: None

Conflicts of interest: None