CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Estradiol (Imvexxy)

Indication: For the treatment of postmenopausal moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy

Sponsor: Knight Therapeutics Inc.

Recommendation: Reimburse with Conditions

Version:	Draft
Publication Date:	December 2021
Report Length:	11 Pages

Single Technology

CADTH

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

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.

ESTRADIOL (IMVEXXY — KNIGHT THERAPEUTICS INC.)

Therapeutic Area: Dyspareunia

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that softgel estradiol vaginal insert (Imvexxy) be reimbursed for the treatment of postmenopausal moderate to severe dyspareunia, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase 3, randomized, double-blind, placebo-controlled study (REJOICE) comparing the efficacy and safety of softgel estradiol vaginal inserts with placebo in postmenopausal women with moderate to severe dyspareunia was reviewed by CDEC. The REJOICE study demonstrated that treatment with softgel estradiol vaginal inserts (both 4 mcg and 10 mcg doses) compared to placebo led to statistically significant improvement on each of the 4 co-primary endpoints: 1) increase in the percentage of vaginal superficial cells, 2) decrease in the percentage of vaginal parabasal cells and 3) decrease in the percentage vaginal pH, and 4) decrease in severity of the most bothersome symptoms (MBS) of dyspareunia associated with vulvar and vaginal atrophy (VVA) (as measured by the VVA Symptoms Self-Assessment Questionnaire).

The clinical expert identified an unmet need for patients who do not respond to available treatments for dyspareunia or who find application of treatment options difficult, uncomfortable or messy. However, no evidence was included to demonstrate softgel estradiol vaginal insert would meet this need. Given that no direct or indirect clinically relevant comparative evidence between the softgel estradiol vaginal insert and the other vaginal estrogen therapies in postmenopausal women with moderate to severe dyspareunia was available for this review, the potential benefit of the softgel estradiol vaginal insert compared with other treatments currently reimbursed in Canada remains unknown.

At the sponsor submitted price for softgel estradiol vaginal insert and publicly listed prices for comparators, softgel estradiol vaginal insert was less costly compared with tablet estradiol vaginal insert. However, compared with estrone and conjugated estrogen cream, softgel estradiol vaginal insert ranged from cost savings to increased costs depending on the dose of the cream-based comparator.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Reimburse in a similar manner to currently funded vaginal estrogen products.	No robust evidence was reviewed to support a clinical benefit for softgel estradiol vaginal insert compared with other vaginal estrogen therapies.
Pricing	
2. The cost of softgel estradiol vaginal insert should be negotiated to provide cost savings for drug programs relative to the least costly local hormone therapy reimbursed for the treatment of individuals with postmenopausal moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy.	At its submitted price softgel estradiol vaginal insert was cost saving in comparison with tablet estradiol vaginal insert and more expensive than the least costly local hormone therapy reimbursed for postmenopausal moderate to severe dyspareunia. There is insufficient evidence to suggest the softgel estradiol vaginal insert fulfills an unmet need in comparison with the least expensive local hormone therapy reimbursed for postmenopausal moderate to severe dyspareunia.

Discussion Points

- CDEC discussed that moderate to severe dyspareunia is a symptom of VVA and that other vaginal estrogen products are reimbursed by most public drug plans for broader symptoms of VVA. The clinical expert indicated that softgel estradiol vaginal insert would likely be used beyond the Health Canada indication in this broader patient population (i.e., postmenopausal women with other VVA-related symptoms such as vaginal dryness) in clinical practice.
- CDEC noted that according to the clinical expert, not all patients respond to currently available treatments for dyspareunia, and that some treatment options are difficult, uncomfortable, or messy to administer. CDEC also discussed the pragmatic advantages of a softgel preparation compared to other formulations of vaginal estrogen therapies (e.g., tablet, ring, cream). However, no evidence on ease and acceptability of use was included to demonstrate softgel estradiol vaginal insert would meet this need. There was no input provided by clinician or patient groups.
- CDEC discussed pricing of softgel estradiol vaginal insert given the lack of clinically relevant direct and indirect comparative evidence between estradiol vaginal insert and the other vaginal estrogen therapies in postmenopausal women with moderate to severe dyspareunia and the lack of long-term efficacy and safety data beyond 12 weeks. Given these gaps in evidence, CDEC was not able to conclude whether the softgel estradiol vaginal insert offered clinical benefit over currently available treatments.
- CDEC also discussed other doses of softgel estradiol vaginal insert (8 mcg [2 x 4mcg] and 14 mcg [4 mcg +10 mcg]) based on input from Drug Plans and noted that dose escalation from 4 mcg to 8 mcg or 14 mcg may occur in a small proportion of patients and acknowledged the uncertain benefit of dose escalation from 4 mcg to 8 mcg or 14 mcg and potential impact on cost savings depending on the comparator of interest.
- CDEC noted that according to the clinical expert, treatment response would be assessed at 3-6 months following initiation and again at 6-12 months, then yearly thereafter. CDEC discussed whether softgel estradiol vaginal insert should be continued as long as needed for symptom management as symptoms may recur upon discontinuation and noted that currently available products in Canada of the same indication do not have limitations on treatment length.
- CDEC noted that softgel estradiol vaginal insert should not be used in combination with other vaginal estrogen products.

Background

The estradiol vaginal insert has a Health Canada indication for the treatment of postmenopausal moderate to severe dyspareunia, one of the key symptoms of vulvovaginal atrophy (VVA). It is available as 4 mcg and 10 mcg 17β-estradiol and is used intravaginally. According to the product monograph, treatment with estradiol vaginal insert should start at the 4 mcg dosage strength, with dosage adjustment guided by the clinical response. The initial dose is 1 vaginal insert daily at approximately the same time for 2 weeks. The maintenance dose is 1 vaginal insert twice weekly, every three to four days.

The sponsor's reimbursement request was the same as the Health Canada-approved indication.

Sources of Information Used by the Committee

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

- A review of one RCT in postmenopausal women with moderate to severe dyspareunia
- Input from public drug plans that participate in the CADTH review process
- One clinical specialist with expertise diagnosing and treating patients with vaginal pain symptoms
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

The clinical expert indicated that not all patients respond to the available treatments for dyspareunia. Some treatment options are difficult, uncomfortable, or messy to administer. Some women are reluctant to initiate hormonal treatment due to the safety concerns regarding exogenous hormone therapy.

Most menopausal women with VVA-related symptoms are likely to benefit from vaginal estrogen therapy. In the clinical expert's opinion, the estradiol vaginal insert is another form of existing medication for treatment of VVA, including dyspareunia. It would be used as a first-line treatment or after failure on other treatments for women who are suitable to receive estrogen replacement for VVA.

The clinical expert also indicated that in clinical practice, treatment response is assessed based on patient's self report of improvement in symptoms. This is a clinically meaningful outcome measure. The expert suggested treatment response be assessed at 3-6 months following initiation of treatment, and again at 6-12 months, then yearly thereafter if continued treatment is required.

Estradiol vaginal inserts are likely prescribed in an outpatient ambulatory clinic setting by family physician or gynecologist. The drug can be self-administered by the patient in her own home.

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 softgel estradiol vaginal insert:

- Considerations for initiation of therapy
- Considerations for prescribing of therapy
- Generalizability of trial populations to the broader populations in the jurisdictions
- System and economic issues

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

Table 2. Responses to Questions from the Drug Programs

Additional Implementation Questions from the Drug Programs	
Implementation Issues	**Advice from CADTH**
Relevant Comparators	
No evidence comparing efficacy and safety vs. currently-funded vaginal estrogen products. Comparisons to placebo (Phase 3, REJOICE) and tablet estradiol vaginal insert 10 mcg (in a PK study) only.	CDEC noted that there is only one trial (REJOICE) that compared softgel estradiol vaginal insert to placebo demonstrating superiority in reducing severity of dyspareunia and one PK study comparing to tablet estradiol vaginal insert 10 mcg demonstrating lower systemic exposure for softgel estradiol vaginal insert. CDEC acknowledged that therapy selection may be based on application acceptability and patient preference, however, CDEC felt that overall there is inadequate information to guide the selection of softgel estradiol vaginal insert over tablet estradiol vaginal insert or the other vaginal estrogen products given the lack of comparative evidence.
Other vaginal estrogen products (e.g., tablet estradiol vaginal insert 10 mcg, conjugated estrogens vaginal cream) are listed as an open benefit under most public plans, except in British Columbia where tablet estradiol vaginal insert is not reimbursed.	CDEC acknowledged open benefit listings for other vaginal estrogen products under most public plans (except in British Columbia where tablet estradiol vaginal insert is not reimbursed).
Considerations for Initiation of Therapy	
Other vaginal estrogen products (e.g., tablet estradiol vaginal insert 10 mcg, conjugated estrogens vaginal cream) were not reviewed by CADTH but are listed as an open benefit under most public plans; therefore, consider criteria which indicates to “reimburse in a similar manner to currently-funded vaginal estrogen products”.	CDEC acknowledged and agreed to recommend reimbursement of softgel estradiol vaginal insert in a similar manner to currently funded vaginal estrogen products.
Considerations for Prescribing of Therapy	
In the product monograph of softgel estradiol vaginal insert, it indicates that “generally, women should be started at the 4 mcg dosage strength. Dosage adjustment should be guided by clinical response”. 1. What proportion of patients may not respond to 4 mcg dose and need to escalate to 10 mcg? 2. How long would the 4 mcg dose be tried before escalating the dose? While the 4 mcg and 10 mcg estradiol inserts are priced the same, the total drug cost of softgel estradiol vaginal insert vs. tablet estradiol vaginal insert could be higher when accounting for patients who were unresponsive to the 4 mcg dose and needed to titrate up to 10 mcg. Would dose escalation to 8 mcg (i.e., 2 x 4 mcg inserts) or 14 mcg (i.e., 4 mcg + 10 mcg) occur in practice? If so, what proportion of patients would need these doses? Total drug cost would be double at these doses.	CDEC noted that the clinical expert estimated that half of the patients need to escalate to the 10 mcg dose. According to the clinical expert, the 4 mcg dose would be used for 3 to 4 months before escalating to the 10 mcg dose if symptoms have not improved at that time. CDEC discussed that dosing of 2 vaginal inserts at a time (8 mcg or 14 mcg) is outside what is recommended in the product monograph. According to the clinical expert, dose escalation (from 4 mcg to 8 mcg or 14 mcg) would only be used in women unresponsive to usual dosage, and following a discussion of risk and benefits. The expert estimated that only a small proportion of these patients would use higher dose (8 mcg or 14 mcg), as this is not the standard treatment regimen with uncertain benefit.

Additional Implementation Questions from the Drug Programs	
Implementation Issues	**Advice from CADTH**
Generalizability	
Is there any reason to believe that softgel estradiol vaginal insert could not be used more broadly, for example, in patients with other causes of estrogen deficiency and/or for symptoms of vaginal atrophy, other than dyspareunia? • softgel estradiol vaginal insert is indicated for the treatment of postmenopausal moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy. Tablet estradiol vaginal insert is indicated for the treatment of the symptoms of vaginal atrophy due to estrogen deficiency. Given the differences in HC-approved indication between softgel estradiol vaginal insert and tablet estradiol vaginal insert, and other vaginal estrogen products are listed as an open benefit under most public plans, consider criteria which indicates to "reimburse in a similar manner to currently-funded vaginal estrogen products".	CDEC noted that dyspareunia is one of the VVA-related symptoms in postmenopausal women. CDEC discussed that although the Health Canada-approved indication for softgel estradiol vaginal insert is "for the treatment of postmenopausal moderate to severe dyspareunia is one of the VVA-related symptoms in postmenopausal women", the clinical expert indicated that softgel estradiol vaginal insert would be considered for use in a broader population – postmenopausal women with other VVA-related symptoms, such as vaginal dryness, are likely to benefit from vaginal estrogen therapy (e.g., estradiol insert) in clinical practice. As a result, CDEC agreed to reimburse softgel estradiol vaginal insert in a similar manner to currently funded vaginal estrogen products.
System and Economic Issues	
The sponsor expects that softgel estradiol vaginal insert will displace market share primarily from tablet estradiol vaginal insert, as it's the most similar comparator used to treat dyspareunia in terms of formulation and administration. Compared to available treatments, the cumulative 3-year budget impact was savings of $649,340. Tablet estradiol vaginal insert is not funded in BC.	The clinical expert indicated it is reasonable to assume that of the market softgel estradiol vaginal insert captures, 99% is from tablet estradiol vaginal insert, given the similarity in formulation and administration.
Confidential negotiated prices may exist for tablet estradiol vaginal insert, conjugated estrogens vaginal cream and estradiol vaginal ring. If there is a lack of evidence to demonstrate superiority of softgel estradiol vaginal insert vs. comparators, consider pricing condition that drug plan cost for softgel estradiol vaginal insert not exceed the drug plan cost of least costly vaginal estrogen product	CDEC highlighted that there is a lack of evidence against comparators and uncertainty with respect to the confidential negotiated prices of the comparator products. As a result, CDEC has recommended the price of softgel estradiol vaginal insert be negotiated to provide cost savings in comparison with the least costly vaginal estrogen product.

Clinical Evidence

Pivotal Studies

Description of studies

One phase III study (REJOICE, N = 574) was submitted to support the clinical benefit of estradiol vaginal inserts. The trial enrolled postmenopausal women with moderate to severe symptoms of vaginal pain associated with sexual activity.

The REJOICE study was a double-blind, placebo-controlled RCT that assessed the efficacy and safety of estradiol vaginal insert for the treatment of postmenopausal moderate to severe dyspareunia. Eligible patients were randomized to receive estradiol vaginal insert 4 mcg, 10 mcg, or 25 mcg, or placebo for 12 weeks. The results for the estradiol vaginal insert 25 mcg group are not reported in this report because this dose is not approved for use. The co-primary efficacy endpoints were 1) change from baseline to Week 12

in percent change in superficial cells compared to placebo, 2) change from baseline to Week 12 in percent change in parabasal cells compared to placebo, 3) change from baseline to Week 12 in percent change in pH compared to placebo, and 4) change from baseline to Week 12 on the severity of the most bothersome symptoms (MBS) of dyspareunia (vaginal pain associated with sexual activity) associated with VVA (using the VVA Symptoms Self-Assessment Questionnaire) compared to placebo. The average age of the women participating in REJOICE was 59-60 years. The majority of the women were White (86-88%). Gynecological history was similar across treatment groups, except that more patients in the estradiol 4 mcg or 10 mcg groups had prior hysterectomy (46-47% with estradiol vs. 39% with placebo), bilateral oophorectomy (26-27% vs. 21%) and surgical menopause (39-40% vs. 34%). The mean time since menopause was 13.9 to 14.2 years and prior hormone replacement therapy was used in 17.6% to 19.3% of women. Baseline assessments of parabasal cells, superficial cells, vaginal pH and severity of MBS of dyspareunia were similar across treatment groups. For study participation, patients needed to identify that their MBS was moderate to severe dyspareunia. The mean baseline severity score for dyspareunia across treatment groups was 2.6 to 2.7.

Efficacy Results

After three months treatment, the REJOICE study met its objective by demonstrating improvement in favor of both doses of the estradiol vaginal inserts versus placebo on the four co-primary endpoints: change from baseline to Week 12 in the percentage of parabasal cells, superficial cells, vaginal pH, and severity of dyspareunia. One of the outcomes was the change from baseline in patient-reported severity of dyspareunia, which was consistent with clinical practice, according to the clinical expert.

At Week 12, vaginal dryness was improved with both doses of estradiol vaginal insert compared with placebo, while only the estradiol 10 mcg group had improved vulvar and/or vaginal itching or irritation versus placebo. The expert indicated that the results of these secondary efficacy outcomes were consistent with the primary outcomes, which favoured estradiol over placebo; however, the differences between estradiol and placebo may not be considered clinically important.

According to the clinical expert, patient-reported symptom relief is a clinically relevant outcome in the study population. In REJOICE, a VVA Symptoms Self-Assessment Questionnaire was used to self-assess patient's symptoms of VVA, including vaginal pain associated with sexual activity, vaginal dryness, and vulvar and/or vaginal itching or irritation. However, no information was provided in the submission describing the validity and reliability of this questionnaire, nor was a MCID reported in the indicated population. Although estradiol vaginal inserts appeared to be efficacious versus placebo, it is difficult to determine whether the magnitude of benefit observed is clinically significant.

Severity of VVA (no atrophy, mild, moderate and severe atrophy) was evaluated using a vaginal mucosa assessment scale, which examines vaginal secretions, epithelial integrity, epithelial surface thickness and color during pelvic examination. Normal vaginal secretions, epithelial integrity, epithelial surface thickness and color at Week 12 were more likely to be observed in patients treated with estradiol (4 mcg and 10 mcg) compared to placebo. However, there was no information provided for the relationship between change in vaginal mucosa and improvement in symptoms, health-related quality of life (HRQoL) or sexual health. Therefore, it is unknown how these changes in vaginal mucosa translate to clinical benefits in the indicated population.

Treatment with estradiol vaginal insert was associated with improved sexual function in postmenopausal women, measured by the Female Sexual Function Index (FSFI). The 10 mcg of estradiol showed statistically significant improvements in Total Score, Lubrication and Pain. There were no statistically significant differences between estradiol 4 mcg and placebo.

Harms Results

During the 3-month study period, the frequency of treatment-emergent adverse events (AEs) was similar between two doses of estradiol vaginal insert and placebo: estradiol 4 mcg 50.8%, estradiol 10 mcg 49.2% and placebo 57.8%. Commonly reported AEs were nasopharyngitis, upper respiratory tract infection, back pain, headache, vaginal discharge, and vulvovaginal pruritus. Patients in the placebo group were more likely to report vaginal discharge and vulvovaginal pruritus compared to the estradiol groups. Three patients in the estradiol 10 mcg group reported serious adverse events (SAEs), while no SAEs were reported in the estradiol 4 mcg and placebo groups. The frequency of withdrawal due to adverse events (WDAEs) was 1.0%, 1.6% and 2.6% in the estradiol 4 mcg group, estradiol 10 mcg group and placebo, respectively. In terms of AEs of particular interest for the review, the frequency of vaginal hemorrhage, cervical dysplasia, and breast mass was numerically higher in the placebo group compared with estradiol groups.

Critical Appraisal

In the REJOICE study, differences were noted in the patients' baseline characteristics between 4 mcg and 10 mcg estradiol inserts and the placebo group. The data suggest that more patients in the estradiol inserts groups had a hysterectomy and bilateral oophorectomy, therefore a higher proportion of these patients were surgically menopausal, compared to those in the placebo group. It is unknown whether patients with surgical menopause will respond differently than those with natural menopause, and whether these imbalances would affect interpretation of the results.

Both subjective (e.g., self-reported symptom relief or change in sexual function) and objective efficacy outcomes (e.g., change in percentage of superficial cells, vaginal pH) were evaluated in the REJOICE study. Although self-reported outcomes are considered clinically relevant in practice to measure treatment response according to the clinical expert, there are no published MCIDs identified for such outcome measures in postmenopausal women. Therefore, it is unclear whether the scales used and the reported between-group differences are clinically meaningful.

Multiplicity was controlled for in REJOICE based on a closed fixed sequence serial testing procedure, with the 4 co-primary endpoints being included. Outcomes outside of the testing hierarchy, such as HRQoL (measured with FSFI), should be viewed as supportive evidence for the overall effects of estradiol vaginal inserts and need to be interpreted with caution, due to the possible inflated type 1 error.

This was a 3-month study, therefore long-term safety (on endometrium and breast, or in general) and efficacy data are unavailable for the two doses of estradiol vaginal inserts. There is a lack of direct or indirect evidence from the included evidence to demonstrate comparative efficacy and safety of estradiol vaginal insert versus other local hormonal therapy in the study population.

Indirect Comparisons

No indirect treatment comparisons were identified for this review.

Other Relevant Evidence

No other relevant studies were identified for this review.

Other Considerations

A bioavailability study compared 10 mcg dose of softgel estradiol vaginal insert with another vaginal estrogen therapy (10 mcg dose of tablet estradiol vaginal insert) in healthy postmenopausal women. The results suggested that the extent of systemic exposure of estradiol 10 mcg was statistically significantly lower than that of tablet estradiol vaginal insert 10 mcg. The lack of comparative safety data between these makes it unknown at present whether there are differences in the safety profiles in the indicated population.

Economic Evidence

Cost and Cost-Effectiveness

At the submitted price of $3.63 per tablet insert, softgel estradiol vaginal insert costs $414 per patient annually in the first year of use and $377 in subsequent years of use. CADTH conducted a re-analysis of the sponsor submitted cost comparison, considering: all relevant local hormone therapies; costs in the first and subsequent years of use; and the lowest available list price for conjugated estrogen cream and the estradiol ring. The annual cost or cost savings with softgel estradiol vaginal insert depend on the choice of comparator. Compared with the existing tablet estradiol vaginal insert, annual cost savings with softgel estradiol vaginal insert were $78 per person in the first year and $71 per person in subsequent years of use. Compared with cream-based comparators, annual per person incremental costs ranged from cost savings of $450 to increased costs of $338, depending on the dose of the cream-based comparators. The incremental cost compared with the estradiol ring was $115 in first year and $79 in subsequent years of use. The incremental costs were calculated based on publicly available list prices of comparators and may not reflect actual prices paid by Canadian public drug plans. Additionally, the price of conjugated estrogens vaginal cream and the estradiol vaginal ring comparator varies across jurisdictions, and as such, incremental costs will vary across jurisdictions.

The cost comparison assumes clinical similarity between softgel estradiol vaginal insert and the other local hormone therapies included in the analysis. Based on a sponsor submitted bioequivalence study, the 10 mcg dose of softgel estradiol vaginal insert is likely clinically similar to tablet estradiol vaginal insert at the same dose in healthy postmenopausal women. The clinical review

conducted by CADTH noted that there was a lack of direct or indirect clinical evidence comparing softgel estradiol vaginal insert to local hormone therapies in the indicated population (menopausal women with dyspareunia). As a result, the cost comparison with tablet estradiol vaginal insert is likely appropriate, while the appropriateness of the cost comparison with the cream and ring based local hormone therapies is associated with uncertainty.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: uncertainty in the estimated market size of the target population and in the anticipated market uptake of softgel estradiol vaginal insert, as well as a reliance on publicly available listed prices for included comparators. CADTH did not conduct base case reanalyses, instead accepting the sponsor's estimated budgetary savings associated with the reimbursement of softgel estradiol vaginal insert of $649,340 over three years including drug costs, markups, and dispensing fees. However, the presence of confidential prices paid by the jurisdictions is likely to reduce or eliminate these savings, depending on the discounts in place.

Canadian Drug Expert Committee (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: November 24, 2021

Regrets

Three expert committee members did not attend

Conflicts of Interest

None