CADTH

CADTH REIMBURSEMENT REVIEW

# Stakeholder Feedback on Draft Recommendation

**ESTRADIOL (Imvexxy)**

(Knight Therapeutics Inc.)

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

**January 7, 2021**

CADTH

# CADTH Reimbursement Review

# Feedback on Draft Recommendation

| Stakeholder information | |
|---|---|
| CADTH project number | SR0694 |
| Name of the drug and Indication(s) | Estradiol (Imvexxy) for the treatment of postmenopausal moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy |
| Organization Providing Feedback | FWG |

| **1. Recommendation revisions**<br>Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation. | | |
|---|---|---|
| **Request for Reconsideration** | **Major revisions:** A change in recommendation **category** or patient **population** is requested | ☐ |
| | **Minor revisions:** A change in reimbursement **conditions** is requested | ☐ |
| **No Request for Reconsideration** | **Editorial revisions:** Clarifications in recommendation **text** are requested | ☐ |
| | **No requested revisions** | X |

| **2. Change in recommendation category or conditions**<br>Complete this section if major or minor revisions are requested |
|---|
| Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation. |

| **3. Clarity of the recommendation**<br>Complete this section if editorial revisions are requested for the following elements |
|---|
| **a) Recommendation rationale** |
| Please provide details regarding the information that requires clarification. |
| **b) Reimbursement conditions and related reasons** |
| Please provide details regarding the information that requires clarification. |
| **c) Implementation guidance** |
| Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here. |

# Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

| **Algorithm and implementation questions** |
|---|
| **1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)** |
| 1.<br>2. |
| **2. Please specify other implementation questions or issues that should be addressed by CADTH** |
| 1.<br>2. |
| **Support strategy** |
| **3. Do you have any preferences or suggestions on how CADTH should address these issues?** |
| May include implementation advice panel, evidence review, provisional algorithm (oncology), etc. |

# CADTH Reimbursement Review
# Feedback on Draft Recommendation

| Stakeholder information | |
|---|---|
| CADTH project number | SR0694 |
| Brand name (generic) | Estradiol |
| Indication(s) | For the treatment of postmenopausal moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy |
| Organization | Knight Therapeutics Inc. |
| Contact information[a] | Name: [redacted]<br>Email: [redacted]<br>Phone: [redacted]<br><br>Name: [redacted]<br>Email: [redacted]<br>Phone: [redacted] |

| Stakeholder agreement with the draft recommendation | | |
|---|---|---|
| **1. Does the stakeholder agree with the committee's recommendation.** | Yes | ☒ |
| | No | ☐ |

*Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.*

| Expert committee consideration of the stakeholder input | | |
|---|---|---|
| **2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?** | Yes | ☐ |
| | No | ☒ |

*If not, what aspects are missing from the draft recommendation?*

While we believe the major aspects of our submissions were considered by CADTH, we do believe the following clinical assessment for Imvexxy was not wholly assessed in the draft recommendation:

**Vaginal Mucosa and Symptom Improvement**

The reviewer made the following comment regarding vaginal mucosa and symptom improvement: "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." (p.8 of the Draft Recommendation)

In fact, there is information linking the change in vaginal mucosa and disease symptoms and objective and subjective measures of vulvar and vaginal atrophy (VVA). The response of the vaginal mucosa with Imvexxy and its correlation with VVA symptoms was examined as well as whether visual examination is a useful measure for assessing VVA. Significant improvements were observed with both Imvexxy doses (4mcg and 10mcg estradiol) versus placebo in vaginal color, epithelial integrity, epithelial surface thickness, and secretions for all comparisons at all time points. Additionally, Pearson's correlations and logistic regression receiver-operating characteristic curve analyses

significantly correlated the sum of the individual visual assessment scores with dyspareunia (P<0.0001) and vaginal dryness (P<0.0001) at 12 weeks (1).

Correlations between the objective and subjective measures of VVA have been previously evaluated (2,3). For instance, a vaginal pH>6.0 measured at the mid vagina correlated with elevated levels of parabasal cells. Visual assessments of vaginal atrophy using the Vaginal Physical Examination Scale also significantly correlated with vaginal pH and the maturation index score. Likewise, correlations were observed using the visual assessment scoring in the phase 2 pilot trial of Imvexxy, which showed significant correlations with the change from baseline to day 15 for percentage of vaginal cells and vaginal pH (r=0.35, P=0.02) with the sum of the four visual assessments (4). The receiver operating characteristic curve analyses showed that visual assessment summary scores had good sensitivity and specificity to detect moderate-to-severe dryness or dyspareunia. Since visual inspection of the vagina with the 4-point assessment tool showed moderate positive correlation with dyspareunia and vaginal dryness in this study, this tool may help healthcare professionals diagnose VVA and assess its treatment, and provide a vehicle for healthcare professionals to initiate discussion with their patients who are not comfortable talking about their sexual health.

Thus, we kindly request CADTH recognize that the relationship between change in vaginal mucosa and symptom improvement has been previously documented in literature and was also studied for IMVEXXY where the results were peer reviewed and published. Therefore, we request the removal of the following identified wording on page 8 of the draft recommendation: “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.”

| **Clarity of the draft recommendation** | | |
|---|---|---|
| **3. Are the reasons for the recommendation clearly stated?** | Yes | ☒ |
| | No | ☐ |
| *If not, please provide details regarding the information that requires clarification.* | | |
| **4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?** | Yes | ☒ |
| | No | ☐ |
| *If not, please provide details regarding the information that requires clarification.* | | |
| **5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?** | Yes | ☒ |
| | No | ☐ |
| *If not, please provide details regarding the information that requires clarification.* | | |

[a] CADTH may contact this person if comments require clarification.

## References


1. Simon, J. A., Archer, D. F., Kagan, R., Bernick, B., Graham, S., Constantine, G. D., & Mirkin, S. Visual improvements in vaginal mucosa correlate with symptoms of VVA: data from a double-blind, placebo-controlled trial. Menopause, 24(9), 1003–1010.
2. Brizzolara S, Killeen J, Severino R. Vaginal pH and parabasal cells in postmenopausal women. Obstet Gynecol 1999;94:700-703.
3. Greendale GA, Zibecchi L, Petersen L, Ouslander JG, Kahn B, Ganz PA. Development and validation of a physical examination scale to assess vaginal atrophy and inflammation. Climacteric 1999;2:197-204.

4. Constantine GD, Kushner H, Bernick B, Graham S, Mirkin S. Vaginal physical examination correlates with vaginal epithelial cells and pH and can be used to assess treatment efficacy. Presented at the Annual Meeting of the Endocrine Society, March 5-8, 2015, San Diego, CA.