CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

estradiol and progesterone (Bijuva)

(Knight Therapeutics Inc.)

Indication: Vasomotor symptoms associated with menopause

January 27, 2022

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0697
Name of the drug and Indication(s)	Estradiol and Progesterone Capsule (Bijuva) for the treatment of moderate to severe vasomotor symptoms associated with menopause in women with intact uterus
Organization Providing Feedback	FWG

1. Recommendation revisions 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 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 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. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 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	SR0697
Brand name (generic)	Estradiol and progesterone
Indication(s)	For the treatment of moderate to severe vasomotor symptoms associated with menopause in women with intact uterus
Organization	Knight Therapeutics Inc.
Contact information[a]	Name: [redacted] Email: [redacted] Phone: [redacted] Name: [redacted] Email: [redacted] 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 Bijuva requires additional clarification in the draft recommendation:

Progesterone Exposure

The draft recommendation states the following language, "In this study, the AUC0-8 estradiol/progesterone capsule AUC0-t and for baseline-adjusted and unadjusted estradiol and total estrone showed bioequivalence to the Reference product but progesterone exposure for the estradiol/progesterone capsule was significantly lower than the Reference product for all PK parameters." (p. 9 of Draft Recommendation under the Bioequivalence section)

It should be noted that the two initial bioequivalence (BE) studies were single dose pharmacokinetic (PK) studies to compare the bioavailability of estradiol/progesterone capsule 2 mg E2/200 mg P with the same doses of Estrace (estradiol tablets USP) and Prometrium (progesterone USP) in healthy, adult, postmenopausal female subjects. In one of these studies, administration of study drug was under fasting conditions (Study 351) and in the other study, study drug was administered 30 minutes after the start of a high-fat, high-calorie meal (Study 352).

Under fasting conditions (Study 351), the progesterone exposure for the estradiol/progesterone capsule was significantly lower than the Reference for all primary PK parameters. However, under high-fat fed conditions (Study 352), all of the primary PK parameters for progesterone, as well as other parameters for estradiol and its metabolites, were higher for the estradiol/progesterone capsules than the Reference in most cases. Due to the intrasubject coefficient of variation being > 30% in many cases, a reference-replicated, reference-scaled, BE approach was taken in Study 459 under high-fat, high-calorie fed conditions. Results showed that estradiol, estrone (free and total), and progesterone plasma concentrations were BE to the same doses of Estrace and Prometrium under high-fat fed conditions.

As such, the dosing recommendation included in the Bijuva Product Monograph is to take the capsule each evening with food.

Based on the results from these studies, we request CADTH clarify the text in the report to reflect that progesterone exposure was only lower for estradiol/progesterone capsules in a fasted state study. Under fed conditions, progesterone and estradiol exposure from estradiol/progesterone tablets were comparable to that of the Reference product.

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.