CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

PRASTERONE (Intrarosa)

(Lupin Pharma Canada Ltd.)

Indication: For treatment of postmenopausal vulvovaginal atrophy.

March 31, 2022

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0707-000
Brand name (generic)	Intrarosa (Prasterone) DHEA Vaginal Ovules
Indication(s)	Treatment of GSM (Genitourinary Syndrome of Menopause) / Vulvovaginal Atrophy)
Name of Clinician Group	Reproductive Endocrinology / EMBC (Early Menopause & Bones Clinic) & Clinician Specializing in Menopause & Osteoporosis
Contact information[a]	Christine M Derzko MD, FRCSC

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☒

I agree that Prasterone has been shown to be an effective treatment for GSM (genitourinary syndrome of menopause). Many clinical trials and reviews are cited in the report, and as such it should be considered as an excellent alternative treatment .

The concern that arises is accessibility for some patients for whom by their own choice or based on their clinical situation eg history of or increased breast ca risk, prasterone would be the optimal first choice therapy. Not having cost coverage would have the effect of patients choosing another, perhaps less ideal vaginal GSM therapy, or avoiding treatment altogether.

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	☐

Prasterone both from data summarized from clinical trials (in several of which I was a clinical investigator) and in accumulated "real world data´ from jurisdictions where it is in use, have shown efficacy in the treatment of GSM
In addition,the body of evidence supporting the safety of prasterone ie the unique action by which DHEA achieves its effect in correcting GSM should be considered.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
The proposed reimbursement of prasterone is based on the much lower cost of an alternative very effective treatment, Premarin cream as the comparator. In our discussions, many of us feel that a better comparator would be Vagifem, a twice weekly vaginal tablet inserted using an applicator—as it is which is much more like the insertion of Prasterone, an ovule used daily, which also uses an applicator for insertion. For many women the convenience & acceptability of using an applicator carrying a pill or ovule is greater than the use of a vaginal cream. Thus we recommend your consideration of Vagifem rather than Premarin vaginal cream, as the cost comparator.: the calculated cost difference of reimbursement would be less.	No	☐

If not, please provide details regarding the information that requires clarification. (see summary below)		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes No	☒ ☒
Yes the comparison to Premarin vaginal cream has been clearly stated and the calculation done. Please consider a comparison calculation with Pasterone vs Vagifem		
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. YES – reimbursement conditions are clearly stated, but we recommend re-consideration for the reasons noted below		

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

SUMMARY : re our recommendations:

1) **GSM (genitourinary syndrome of menopause) or vulvovaginal atrophy is a common estrogen deficiency problem notably in the postmenopausal age group, which when left untreated may result in significant long term consequences.**
2) **GSM treatment is aimed at correcting the local genitourinary tissue estrogen deficiency using local treatments notably vaginal estrogen cream eg twice weekly Premarin vaginal cream; an estrogen containing silastic vaginal ring which is replaced every 3 months i.e. Estring or a twice weekly vaginal estrogen pill inserted using an applicator, namely Vagifem.**
3) **a.Prasterone is an ovule of DHEA, which like Vagifem, is inserted using an applicator, but unlike Vagifem, requires daily use.**
   b.Prasterone is not a vaginal estrogen, but rather is a unique molecule (DHEA) which only in the vagina (but not the endometrium) is converted to estrogen providing a local vulvovaginal estrogen effect in the vagina. However it is not absorbed systemically as estrogen, and thus is without systemic estrogenic effects
   c.This specific property(lack of systemic estrogenic effect) gives it a unique advantage and application eg for use in the treatment of GSM in breast cancer patients on aromatase inhibitors, for which safety data is accumulating.
   d.However Prasterone is also an excellent and ideal treatment for any/all patients with GSM and patients or physicians may choose to use it as primary therapy for GSM or as secondary Rx when other GSM/estrogen products are not medically appropriate or are not acceptable
4) **<u>Reimbursement :</u> The concern is that even when it is decided (either based on patient preference or specific medical direction) that the optimal treatment of a patient's GSM would/should be Prasterone, if reimbursement is not available, patient may simply avoid treating her GSM altogether or may stop treatment leading to a recurrence of her GSM and its complications.**

5) **Therefore, we recommend re-consideration of your proposal for reimbursement of GSM therapies to include Prasterone, an excellent GSM product and to consider it with its closest comparator, Vagifem.**

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0707-000
Brand name (generic)	Intrarosa (Prasterone)
Indication(s)	Intrarosa (Prasterone vaginal ovules) is indicated for treatment of postmenopausal vulvovaginal atrophy.
Organization	Lupin Pharma Canada
Contact information[a]	Name: Michelle Jacobson

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.

I have reviewed the CADTH recommendations and I agree with the clinical review that CADTH has drafted. Where I disagree, however, is with some of the economic related recommendations (specifically, reimbursement conditions) with reasoning detailed as follows:

"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."

In my opinion and as a future prescriber of this product, Intrarosa should be financially compared to Vagifem (vaginal estradiol hemihydrate) tablets and not Premarin (conjugated estrogen cream). These are more similar comparators as insertable solid products that are singular hormonal substances and not a mixed product with several compounds like CE cream. Comparing the price to CE cream will add a barrier to access for Canadian patients. I prescribe Vagifem often and I would consider Intrarosa as a more similar comparator pharmacologically, byy route of administration and in patient profile.

Every woman is unique with different priorities in regards to VVA therapeutic options. I strongly believe that having a wide armamentarium of unique therapeutic options reimbursed allows for patients to have an active role and staying committed to the recommended therapy I advise them to take. VVA treatments are not terribly expensive but can certainly be unaffordable for many, and patient compliance can be low in those that have vulvovaginal atrophy for many reasons linked to the characteristics of a treatment option. It is my opinion that by limiting reimbursement on treatment options that have novelties in route of administration, mechanism of action and routine of use can have consequences to the health outcomes of these patients.

In summary, I feel limiting reimbursement on Intrarosa would impact compliance and possibility the efficacy of this novel treatment. This is especially true in a daily product compared to twice weekly like the comparators. I support preventing long term complications of VVA and decreasing the overall cost to the health care system and thus I would support comparative reimbursement for Intrarosa to that of Vagifem.

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?		
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.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 Michelle Jacobson • Clinician 2 Wendy Wolfman • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Sinai Health

Wendy L. Wolfman, MD, FRCSC, FACOG
Mount Sinai Hospital
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[redacted]

March 30, 2022

To: CADTH Committee

RE: Review for intrarosa (prasterone)

I agree with most of the CADTH review. However I have concerns about lack of access of an option for women who don't respond to local vaginal estrogens. As you are aware, GSM affects 50% of women within 3 years of menopause and 70% by the age of 70. A percentage of women do not respond to moisturizers, lubricants and local estrogens. Other women do not prefer creams or rings or have allergies to medications. A third group may have an estrogen sensitive malignancy and are fearful of the black-box warning.

Therefore I feel it is important that as many options for therapies be available for this huge number of women that we see. Certainly this option should be funded in the same way and at the same reimbursement as the local estrogen tablet, Vagifem.

Prasterone has a unique action that is different from the estrogen products and has additional action at the testosterone receptor. Genitourinary syndrome of menopause results from lack of hormones at multiple levels including the epithelium, lamina propria and muscularis. This is the only approved agent we have currently that addresses multiple levels of the vaginal wall.

In practice, most women use vaginal products in a much lower frequency than we prescribe. Therefore I feel the calculations for the total cost of this medication is not correct.
I hope the committee will reconsider the reimbursement for this important option for menopausal women.

Sincerely,

[redacted]

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0707
Name of the drug and Indication(s)	Prasterone (Intrarosa) for the treatment of postmenopausal vulvovaginal atrophy
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.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0707-000
Brand name (generic)	Intrarosa (prasterone)
Indication(s)	Intrarosa (prasterone vaginal ovules) is indicated for treatment of postmenopausal vulvovaginal atrophy.
Organization	Lupin Pharma Canada Ltd.
Contact information[a]	Name: [redacted] Title: [redacted] Email: [redacted] Phone: [redacted]

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

Lupin Pharma Canada Ltd. (Lupin) agrees with the CADTH draft recommendation's recognition of the clinical benefit associated with Intrarosa (prasterone) in postmenopausal vulvovaginal atrophy (VVA), and the unmet need amongst VVA patients for alternatives to local estrogen therapy. As the recommendation noted, in postmenopausal patients with moderate-to-severe VVA Intrarosa significantly improved dyspareunia, vaginal dryness, percentage of vaginal superficial cells, percentage of vaginal parabasal cells, and vaginal pH. CADTH also noted that local estrogen therapies are contraindicated in many patients (e.g., those with a history of breast cancer), and known severe safety issues with systemic estrogen therapy causes many patients to avoid local estrogen treatment. However, Lupin disagrees with CADTH's selection of comparators in its review of Intrarosa, with the recommended pricing reimbursement condition for Intrarosa, and with the assertion that Intrarosa increases androgen levels in patients.

- **Vagifem (estradiol) is the sole appropriate comparator for Intrarosa; CADTH's inclusion of conjugated estrogen (CE) cream (Premarin), estrone cream (Estragyn), and estradiol ring (Estring) is inappropriate.**

The true appropriate Intrarosa comparator is Vagifem, as Vagifem is the most widely used local hormonal therapy for postmenopausal vulvovaginal atrophy (VVA) in Canada, and Vagifem, like Intrarosa, is administered as an intravaginal tablet. The other hormonal therapies considered to be comparators by CADTH, Estragyn vaginal cream, Estring, and Premarin vaginal cream, serve only a limited role in the treatment of postmenopausal VVA. Premarin usage results in systemic and sustained high levels of estrogen absorption. Estragyn and Premarin vaginal cream are intended for short-term use as per their product monographs, while Estring is intended for use for a maximum duration of 2 years. However, postmenopausal VVA is a long-term, chronic condition. Accordingly, in order for patients to maintain symptom relief, they must be treated on a long-term basis, which Estring, Estragyn, and Premarin are not suitable for. Furthermore, significant safety concerns have been raised with respect to the use of estrogen-based creams such as Premarin for treatment of VVA. In January 2020, the safety committee of the European Medical Agency (EMA) issued a press release recommending that the use of high-strength estradiol creams containing 100 micrograms/gram of estradiol be limited, at most, to a single treatment period of up to 4 weeks due to substantial systemic absorption of estradiol associated with use of these creams. A copy of this

recommendation is enclosed. Although Premarin cream is composed of conjugated estrogens rather than estradiol, its concentration of 625 micrograms per gram is substantially higher than 100 microgram/gram threshold discussed in the EMA recommendation. Furthermore, the product monograph for Premarin warns that there is a risk of systemic absorption with use of Premarin vaginal cream, and treatment with 0.3 mg vaginal Premarin cream has been shown to elicit elevations in estrone levels beyond the reference level in postmenopausal women. Given the high strength of Premarin cream, the recommendation that estrogen-based creams be limited to 4 weeks of treatment further underscores that Premarin is an inappropriate comparator to include in an evaluation of Intrarosa for the treatment of long-term postmenopausal VVA.

- **The condition that the negotiated price of Intrarosa "not exceed the least costly vaginal estrogen product reimbursed for the treatment of postmenopausal VVA" is based on inappropriate comparators and places an excessive burden on Intrarosa even beyond what is required of currently funded vaginal estrogen treatments.**

The recommendation that Intrarosa's price be based on all vaginal estrogen products reimbursed for postmenopausal VVA, includes several products which are inappropriate comparators to Intrarosa for the reasons described above in detail. These treatments are infrequently used, not intended for long-term use, and administered via an entirely different route of administration than Intrarosa. Furthermore, requiring that Intrarosa's price be equivalent to the cheapest of all of these treatments, Premarin cream, inherently means that CADTH is recommending Intrarosa's price be cheaper than Vagifem, Estring, and Estragyn vaginal cream. Thus, this condition puts a restriction on the Intrarosa price greater than what has been required for these non-Premarin treatments. Currently, the majority of patients are treated with reimbursed local hormonal therapies that are not the lowest cost, i.e., are not Premarin cream (in Nov 2021 96% of patients in Canada were treated with treatments other than Premarin cream -- IQVIA). A further concern in benchmarking to the Premarin cream price is that Premarin cream is frequently out of stock due to manufacturing disruptions and as such is not a readily available option for many patients; the latest shortage lasted for 7 months from May 21st to December 7th (https://www.drugshortagescanada.ca/drug/2414). Due to frequent shortages of Premarin cream stock, Premarin is in effect not a legitimate real world comparator and its price should not be used as the basis for the Intrarosa price negotiations. There are much more appropriate currently reimbursed comparators such as Vagifem that treats 89% of all VVA patients in Canada (Nov 2021 – IQVIA). VVA is a chronic illness that needs to be treated chronically; every time there is a drug shortage a treatment switch is required, which results in the healthcare system incurring the additional costs of a physician visit. Moreover, interruptions to treatment can worsen long term patient outcomes, increasing the possibility of outcomes which incur further expenses for the healthcare system.

- **Clinical studies have consistently shown that Intrarosa (prasterone) does not increase circulating androgen levels above normal postmenopausal levels.**

The suggestions that Intrarosa can increase androgen levels (Table 2, page 7 of the draft recommendation) above levels seen in normal postmenopausal women contradicts well-established published clinical findings. The ERC-230 study reported testosterone and dihydrotestosterone (DHT) levels well within normal postmenopausal vulvovaginal atrophy levels after 12 months of prasterone treatment (Ke et al. 2015). Moreover, an integrated analysis of multiple prasterone (Martel et al. 2016) clinical trials further found that the primary androgenic metabolite, serum androsterone glucuronide (ADT-G), remained well within normal postmenopausal ADT-G levels after 12 weeks of treatment. Therefore, Intrarosa treatment does not result in androgen levels increasing relative to the levels seen in normal postmenopausal women.

In conclusion, while Lupin supports the overall recommendation that Intrarosa be reimbursed by the CADTH-participating drug programs, Lupin feels it is important to emphasize that Vagifem is the sole appropriate comparator for Intrarosa. As a result, the recommended pricing reimbursement condition for Intrarosa is excessive given the inclusion of inappropriate comparators, the use of a pricing reference point based on a comparator that is frequently out of stock, and the requirement that Intrarosa be cheaper than the majority of vaginal estrogen therapies for postmenopausal VVA. Finally, Lupin would like to reiterate that it has repeatedly been shown that Intrarosa treatment does not increase androgen levels beyond what is seen in normal postmenopausal women.

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?		

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	☒
No. As stated above, the rationale for the pricing reimbursement condition recommended for Intrarosa by CDEC is not clear. Requiring that Intrarosa be cheaper than all except the cheapest vaginal estrogen therapies inappropriately bases Intrarosa price negotiations on non-comparator estrogen therapies, and subjects Intrarosa to an excessive pricing limitation beyond most reimbursed vaginal estrogen therapies.		

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