CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

CHLORMETHINE GEL (Ledaga)

(Recordati Rare Diseases Canada Inc.)

Indication: The topical treatment of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in adult patients who have received prior skin-directed therapy.

CADTH received stakeholder feedback from:

Provincial Advisory Group Committee

Lymphoma Canada, Canadian Skin Patient Alliance, Cutaneous Lymphoma Foundation (Joint Submission)

Recordati Rare Diseases Canada Inc.

July 22, 2021

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0242
Name of the drug and Indication(s)	Chlormethine hydrochloride for MF-CTCL
Organization Providing Feedback	PAG

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
None.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
None.
b) Reimbursement conditions and related reasons
None.
c) Implementation guidance
None.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0242-000
Brand name (generic)	Ledaga (chlormethine hydrochloride)
Indication(s)	For the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients.
Organization	Lymphoma Canada (LC), Canadian Skin Patient Alliance (CSPA), Cutaneous Lymphoma Foundation (CLF)
Contact information[a]	Name: Kaitlyn Beyfuss-Laski; Email: [redacted]; Phone: [redacted]

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

LC, CSPA and CLF do not agree with pERCs negative recommendation for Ledaga for MF-CTCL. The following lays out our reasoning for disagreeing with the rationale provided by pERC:

1. **High degree of uncertainty regarding the magnitude of the treatment effect.**

Based on the information provided in pERCs report, an increased percentage the CAILS response rate score, percentage of patients achieving a complete response, length of response, SWAT response, and body surface area response was greater in the Ledaga (gel) group compared to the compounded ointment group. Further the time to response was nearly half for patients receiving Ledaga, indicating patients are able to return to their quality-of-life (QoL) faster than patients receiving compounded ointment. The patient experience indicated the majority of patients were able to complete their full treatment course or were still receiving treatment, and treatment side effects did not negatively impact QoL. Further, Ledaga was able to manage patient's MF symptoms including red skin patches (56%), skin itchiness (31%), skin ulcers (15%), and skin pain (15%). Though the magnitude of improvement may be minimal to moderate between the gel treatment and the compounded ointment, there is a large percentage of patients that experience positive outcomes from receiving the gel ointment.

2. **The trial was not designed to evaluate the effects of chlormethine gel on health-related quality of life, which was identified by patients as a key outcome of interest.**

We agree that the clinical trial may not have addressed impacts to patient's QoL, however:

a) The clinical trial was conducted between 2010-2012 when incorporating patient-reported outcomes within trials was not commonly performed. Therefore, reliance on patient feedback can be utilized through the patient experience survey and data shared by the patient groups.

b) QoL information and data can be extrapolated very clearly from the patient submission which utilized a qualitative approach to obtaining patient data related to QoL impacts with the use of Ledaga. Ledaga treatment and administration did not cause any significant negative impacts to patients, nor affected patient's ability to exercise, work/volunteer, spend time with family/friends, and fulfill daily obligations and activities (i.e household chores, etc.). Over 50% of patients found that Ledaga was able to improve their overall health and well-being, 19% of whom stated their life was greatly improved.

3. **No comparative data were available between chlormethine gel and the current standards of care for early-stage MF-CTCL in Canada (i.e., phototherapy, topical retinoids, and topical corticosteroids)**

As the clinical trial was conducted in the USA, where the SOC was chlormethine compounded ointment at the time, the trial did not compare against the standards of care for MF-CTCL in Canada. However, there is ongoing research that has been published assessing efficacy, safety, and health-related QoL in a real-world setting. With the submitted clinical trial for Ledaga showing superiority over compounded ointment, the benefits of the addition

of chlormethine gel to current therapies led to ≥ 50% decrease in body surface area patches from baseline to 12 months in over 40% of patients[1].

For this patient population in Canada, there are not many treatment options available and there are different approaches across provinces due to funding and geographical access. For Stage 1a symptomatic very-minimal patch stage disease, first-line treatment may include topical steroids with higher potency (lyderm or betaderm). These however do not function as a long-term solution given the side-effects associated with long-term topical steroid usage. For patients with lesions covering more body surface area or if topical steroids are no longer effective or appropriate, next line therapy is typically Narrow band UVB 311 light-therapy. Alternative light therapy with PUVA (psoralen with UVA) which penetrates deeper is typically reserved for thicker lesions as it is scarcely available. Both forms of light therapy can cause premature skin aging and predispose sensitive individuals to future skin malignancies. For more refractory disease light therapy can be combined with systemic retinoids or immunotherapy such as Interferon alpha with reported synergistic effects along with topical steroids or chlorethamine gel to manage pruritis and pain. Carmustine, an alkylating agent, may also be available in some provinces. Therefore, though there is no national SOC for MF patients; light therapy would be a possible comparative treatment option, however certain patients are not able to receive this therapy due to:

- Geographical distance to treatment centre. Light therapy is required three times a week for life, and patients not located close to a treatment centre would not be able to afford the time and cost of travel;
- There is a risk for the development of skin cancers like melanoma (especially with UVA therapy), particularly for light skin patients and those prone to cancers.

Systemic therapy options are reserved for patients with more advanced disease stage which would include tumours, nodal or blood involvement or skin symptoms not alleviated with skin directed therapies. First line therapy is typically a systemic retinoid often in combination with light therapy. Targretin has the most evidence for use, but it is not available within Canada; alitretinoin is the retinoid with the most similar pharmacology however it does have known impactful side effects. Radiation therapy may also be given at low doses for individual thick plaques or tumours, and in some patients may delay systemic therapy. Patients who have progressed to more advanced stage disease or have thicker resistant plaques require escalation of therapy. Selection of agent is typically based on side effect profile and drug availability with many only accessible by compassionate access programs or private insurance. Therefore, patients requiring treatments for their skin lesions with refractory or relapsed disease where light therapy is not an option, may only be able to access the much-needed Ledaga therapy through a complicated and often delayed special access program that is not guaranteed.

4. **Chlormethine gel was associated with higher percentages of patients who had serious adverse events and withdrawals due to adverse events, with most events being skin-related**

Adverse events from the clinical trial data were relatively comparable between the gel and compounded ointment, however the patient feedback reported low adverse events, especially related to other treatments. The most difficult to tolerate side-effects related to other treatments included fatigue (42%), hair loss (23%), severe itchiness (40%), and skin burning and pain (35%). Whereas, the side effects experienced with Ledaga included itching (37%), blistering (26%), and colouration (33%) or rash (24%). Further, these side-effects did not negatively impact patient's QoL. 37% of patients were further willing to tolerate side effects of a new treatment if they were short-term (13% were not; remainder were unsure). As the clinical trial data found that there was a much shorter time to response with Ledaga, this matches patient preferences. Only 20% of patients who provided feedback had to stop treatment due to side effects, and 46% of patient rated that the side effects of Ledaga had minimal to no negative impact. The majority of patients did not have any side-effects that impacted their QoL.

Given the clinical trial results and patient feedback received, we disagree with many points listed in the rationale provided for a negative recommendation for this treatment. Ledaga addresses patients needs and provides a good response, with many patients having a good-excellent experience with this therapy and would be willing to take this treatment option again if presented to them. **The patients voice was clear in their support of Ledaga.** This option should be available for patients in Canada, especially with its vast use as a standard of care treatment option for patients in the USA. **Patients deserve better than their current limited options available in Canada.**

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	☒

pERC did not interpret the salient points from the patient feedback submitted correctly as indicated:

1. Paragraph 2 – pg 4; first sentence → this does not clearly differentiate that these are symptoms of MF-CTCL. This sentence is structured in a way that appears that these are the reported side-effects of Ledaga. Please provide clarity based on what is provided from the patient feedback submitted:
   Ledaga managed patient's MF symptoms including red skin patches (56%), skin itchiness (31%), skin ulcers (15%), and skin pain (15%), whereas the most commonly reported side effects of Ledaga treatment included itching (37%), hyperpigmentation (33%), skin blistering (26%), rash (24%), or no symptoms (24%).

In pERCs report, there is no information included on the patients experience with Ledaga, whereas in the patient feedback report provided, over a page of patient feedback related to the side-effects, QoL impacts, and overall experience with Ledaga was provided. This data indicated that patients had a good experience with this therapy, had no impacts to their QoL with treatment, showed improvements to overall health and well-being, and would take this treatment option again if provided to them. Further, the general unmet needs and challenges for this patient community were not addressed apart from the brief information included from the patient group. For example, there are challenges related to utilization of compounded therapies compared to gel formulations:

- Patients must trust that the therapeutic is compounded correctly according to the prescriptors direction
- Only specific pharmacies have the ability to compound therapeutics as special equipment is required to handle this toxic formulation to prevent off-gassing

Further, ointments compared to gels have further impacts to patients including:

- Ointment is very thick and greasy as it is an Aquaphor, and can ruin clothing and bedding
- This formulation is toxic in ointment form to other people and pets
- There are certain places that dermatologists prefer not to prescribe ointments (such as the scalp)

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

Brief rationale statements are provided, but it is not clear what part of the stakeholder and clinical trial results yielded these interpretations to result in a negative recommendation. Stakeholder feedback depicts a very different story. The rationale points should be listed and supportive descriptions provided as to where information is lacking or uncertainty exists. Further, more context should be provided as to the current CTCL treatment landscape, referencing unmet needs, comparative and currently approved treatments, funding, and accessibility.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

1. The magnitude of uncertainty of clinical trial data related to response and adverse effects is not clearly outlined (page 5). Related to each response, please indicate the significance and where uncertainty exists.
2. Implementation issue related to cost was addressed, however there was little to no information about additional implementation issues such as access for patients and storage.
3. A comparison should be provided about how implementation and accessibility may be easier compared to other available treatments for this patient population.
4. It is important to note that provinces such as British Columbia have already developed and utilize protocols for implementation of this therapeutic[2].

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

Please see above.

References

1. Kim, E.J. et al. (2021). The PROVe Study: US Real-World Experience with Chlormethine/ Mechlorethamine Gel in Combination with Other Therapies for Patients with Mycosis Fungoides Cutaneous T-Cell Lymphoma. *American Journal of Clinical Dermatology* 22:407-414.
2. Ho, V. (2019). BC cancer protocol summary for topical mechlorethamine in cutaneous t-cell lymphoma. British Columbia, Canada. Accessed from http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Lymphoma-Myeloma/LYMECHLOR_Protocol.pdf (July 10, 2012)

Appendix 1. Conflict of Interest Declarations for Patient Groups

A. Patient Group Information	
Name	*Kaitlyn Beyfuss-Laski*
Position	*Manager of Patient Programs, Research & Advocacy, Lymphoma Canada (LC)*
Date	*22-07-2021*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☐
	Yes	☒
Patient groups CSPA and CLF provided feedback on the pERC recommendation which was incorporated into this draft feedback submission.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☐
	Yes	☒
Information included in this submission was taken directly from the pERC report and/or initial patient feedback submission to CADTH. Patient groups CSPA and CLF provided assistance in collecting the data for the patient feedback submission via administering the feedback survey to their patient constituents.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. 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**
Recordati	☐	☒	☐	☐
Helsinn Pharmaceuticals	☐	☐	☐	☒

A. Patient Group Information	
Name	*Susan Thornton*
Position	*Chief Executive Officer, Cutaneous Lymphoma Foundation (CLF)*
Date	*22-07-2021*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback

4. Did you receive help from outside your patient group to complete your feedback?	No	☐
	Yes	☒
Patient groups CSPA and LC provided feedback on the pERC recommendation which was incorporated into this draft feedback submission.		
5. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☐
	Yes	☒
Information included in this submission was taken directly from the pERC report and/or initial patient feedback submission to CADTH. Patient groups CSPA and LC provided assistance in collecting the data for the patient feedback submission via administering the feedback survey to their patient constituents.		

C. Previously Disclosed Conflict of Interest

2. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

6. 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**
Recordati	☒	☐	☐	☐
Helsinn Pharmaceuticals	☐	☐	☐	☒

A. Patient Group Information

Name	*Rachael Manion*
Position	*Executive Director, Canadian Skin Patient Alliance (CSPA)*
Date	*22-07-2021*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback

7. Did you receive help from outside your patient group to complete your feedback?	No	☐
	Yes	☒
Patient groups CLF and LC provided feedback on the pERC recommendation which was incorporated into this draft feedback submission.		
8. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☐
	Yes	☒
Information included in this submission was taken directly from the pERC report and/or initial patient feedback submission to CADTH. Patient groups CLF and LC provided assistance in collecting the data for the patient feedback submission via administering the feedback survey to their patient constituents.		

C. Previously Disclosed Conflict of Interest

3. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

9. 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**

n/a	☐		☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0242
Brand name (generic)	LEDAGA (Chlormethine Gel)
Indication(s)	For the topical treatment of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) in adult patients who have received prior skin-directed therapy.
Organization	Recordati Rare Diseases Canada Inc.
Contact information[a]	Name: [redacted] Email: [redacted] Phone: [redacted]

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

The interim recommendation is not supported by the evidence that had been submitted nor the evidence identified in the CADTH Reviewer's Report. The submitted evidence and anticipated place in therapy for LEDAGA aligns with stakeholder input and multiple guidelines recommending the use of chlormethine to manage skin symptom burden for early stage MF-CTCL. The current CADTH draft recommendation is contradictory to its own clinical expert reviewers that concluded there is a net clinical benefit associated with LEDAGA. ***As reported in the Draft Recommendation, the evidence provided within the CADTH submission demonstrates the effectiveness of LEDAGA in patients with early stage MF-CTCL.***

- Confirmed response rate (RR) based on the Composite Assessment of Index Lesion Severity (CAILS) score was **higher for chlormethine gel** than chlormethine ointment (58.5% versus 47.7%) in the intention to treat (ITT) analysis[1]
  - The ratio of the RR of gel to ointment was 1.23 (95% confidence interval [CI], 0.97 to 1.55), meeting the pre-specified criterion for non-inferiority (≥ 0.75 for lower bound of 95% CI). - **favouring chlormethine gel**
  - Please note, although not reported in the draft recommendation, the benefit was even more pronounced in the EE population (patients with no major protocol violations who were on study for at least 6 months): 76.7% for chlormethine gel and 58.9% for chlormethine ointment (ratio 1.301; 95% CI: 1.065–1.609).
- SWAT response was 46.9% for chlormethine gel and 46.2% chlormethine ointment in ITT analysis[1]
  - The ratio of response was 1.02 (95% CI, 0.78 to 1.32) - **favouring chlormethine gel**
- Body surface area response was achieved in 44.6% patients treated with chlormethine gel and 43.1% of patients in the chlormethine ointment group[1]
  - A ratio of response of 1.03 (95% CI = 0.78-1.36) - **favouring chlormethine gel**
- Time-to-response in the chlormethine gel group was 26 weeks versus 42 weeks in chlormethine ointment group - **favouring chlormethine gel**[1]
- Response was maintained in 86% of patients in chlormethine gel group[1]

In all outcomes summarized in the CADTH recommendation, chlormethine gel [LEDAGA] was numerically beneficial relative to chlormethine ointment, demonstrating, at a minimum, LEDAGA would be non-inferior to chlormethine ointment (initial standard of care for MF-CTCL when it was available).

It is important to consider that Chlormethine gel [LEDAGA] was considered non-inferior to chlormethine ointment based on a clinically important response in the CAILS score:

- Endpoints such as the CAILS score have been accepted by regulatory authorities and have been used in the approval for multiple drugs for MF-CTCL in the US and EU[2]
- During protocol development for Study 201, investigators recommended CAILS as the primary endpoint. Many of these investigators were also co-authors of the subsequent consensus statement on design of trials for the study of MF-type CTCL[3]
- The choice of non-inferiority margin in Study 201, was previously established in the literature[4]

LEDAGA is already considered as recommended therapy in treatment guidelines.

- BC Cancer protocols include chlormethine gel for MF-CTCL[5-7]
- International treatment guidelines list topical chlormethine as an effective first line therapy for early stage MF-CTCL, i.e., Stages IA, IB and IIA[8, 9]
- LEDAGA (chlormethine gel) is the skin-directed therapy (SDT) with the **highest level of recommendation** for early-stage MF-CTCL in the 2018 ESMO guidelines[10]
- The British Association of Dermatologists guidelines rate the evidence available for chlormethine gel as at a low risk of bias, and that the study was 'well-conducted' (overall rating of 1+ supporting that chlormethine gel has a robust evidence base[11]

Both Patient and Clinician input into the CADTH review of LEDAGA acknowledged the benefits directly associated with LEDAGA[12]

From the CADTH Patient input:

- Having a choice in treatment options was extremely important to them
- Specific need expressed in the for an accessible and effective treatment

From the CADTH Clinician Input:

- [LEDAGA] May be used to treat lesions refractory to topical corticosteroids or when phototherapy is not accessible or is ineffective
- "The clinicians reported that patients who would benefit most from chlormethine gel include adult patients with IA to IIA stages of MF-CTCL with less than 15% body surface area involvement (Stage IA & IIA < 10%; Stage IB > 10%), and patients with select skin sites involved by MF-CTCL (e.g., hair bearing areas")

The evidence provided within the CADTH submission was the basis for the Health Canada (HC) regulatory approval of LEDAGA, with multiple additional agencies acknowledging the effectiveness of LEDAGA in patients with early stage MF-CTCL.

- FDA approval for Valchlor [LEDAGA] was based on the same non-inferiority study. They noted mechlorethamine (nitrogen mustard) has been used since 1950s and is described in the literature. Both clinical and statistical reviewers reporting that efficacy was demonstrated.[13]
- The EMEA approved LEDAGA based on the same non-inferiority study. They concluded "the results from a clinical trial…comparing the commercial formulation chlormethine gel against an adequate chlormethine comparator" and "These data demonstrate the efficacy and safety chlormethine gel…in term of all important clinical endpoints."[14]

The same evidence base supported a positive NICE recommendation

Other HTA agencies, including a recent NICE assessment concluded with a **positive recommendation**, i.e, that: "Chlormethine gel [LEDAGA] is recommended for early stage MF-CTCL." From the NICE review[15]:

- Chlormethine gel [LEDAGA] has proven efficacy for MF-CTCL without any real comparator. It provides a convenient, effective therapy for those not responding to potent topical steroids, without the need for hospital based treatment nor monitoring
- LEDAGA significantly reduces the burden of patient treatment from the hospital and the improvement in skin allowing patients to return to work/fewer sick days
- Topical chlormethine gel is one of the few licensed treatments available for early stage MF-CTCL (in Canada no other drugs are licensed for early stage MF-CTCL)

- There are clear advantages in using chlormethine gel (LEDAGA) compared to the original nitrogen mustard product, which became impossible to source in the last decade and in addition required expensive extemporaneous preparation in specialist pharmacy units

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	☒

As described above, the recommendation did not align with the evidence provided within the submission. Results from the pivotal study comparing LEDAGA to chlormethine ointment met its objectives demonstrating the efficacy and safety of chlormethine gel in terms of improvements in clinically important endpoints.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

No, as described above, the recommendation contradicts the evidence that clearly demonstrates non-inferiority of LEDAGA to what was considered standard of care (when available). A fact that was recognized as providing evidence of efficacy by HC, FDA, EMA and NICE. Moreover, the conclusion on benefits and harms seems to have been informed by and error in the CADTH reported withdrawals due to AEs. As such the CADTH recommendation seems to contradict the available evidence. We hope this was not influenced by the error in reporting withdrawals due to AE, as given the non-inferiority data and need for effective treatments and the lack of access to the chlormethine ointment, the overall risk benefit of LEDAGA should be considered either net positive or net neutral to available therapies. Considering the high unmet need of MF-CTCL patients in Canada for an effective and accessible treatment, CADTH should reconsider their assessment of the net-clinical benefit associated with LEDAGA and provide a positive listing recommendation.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

Mycosis fungoides-type cutaneous T-cell lymphoma is a rare disease with a limited evidence base for existing treatment options.

It is regrettable that CADTH has not recognized the significant unmet need faced by patients with MF-CTCL and used its own Rare Disease "Considerations for Significant Unmet Need" framework and adopted a recommendation to "Reimburse with Conditions".[16] Despite a general sparsity of high quality evidence in mycosis fungoides-type cutaneous T-cell lymphoma, the British Association of Dermatologists guidelines rate the evidence available for chlormethine gel that is provided by Study 201 as at a low risk of bias, and that the study was 'well-conducted' (overall rating of 1+), supporting **that chlormethine gel has the potential to provide a treatment option with a more robust evidence base for its efficacy and safety in this rare disease**.[11]

There is a significant need for alternative treatments for MF-CTCL and the unmet needs of patients with limited early stage disease. Not having access to LEDAGA will leave patients with limited skin directed choices. Topical steroids have typically been tried by most patients, may improve symptoms in the short term but have significant side effects and risks.[11] Phototherapy is an inconvenient hospital based therapy, exposes the whole skin surface to the effects of UV light and has a finite recommended dose due to carcinogenicity. In addition, the recommendation should not underestimate the effect of COVID-19 on treatment choices. The effect of staff redeployment and self-isolation led to restrictions on phototherapy units. Chlormethine gel provides patients with a therapy which can be applied at home, reducing travel and contact within hospitals.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

Not applicable

References

1. *CADTH PC0242 Ledaga - Draft CADTH Recommendation July 8, 2021*.
2. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early stage cutaneous T-cell lymphoma *Arch Dermatol*. 2001;137:581-593.
3. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol*. Jun 20 2011;29(18):2598-607. doi:10.1200/jco.2010.32.0630
4. Duvic M, et al, . A phase III, randomized, double-blind, placebo-controlled study of peldesine (BCX-34) cream as topical therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol*. 2001;44:940-947.
5. BC Cancer. Mechlorethamine drug monograph. Available at: <http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Mechlorethamine_interim%20monograph.pdf.>[Last accessed: 26/06/2020]. 2019;
6. BC Cancer. BC Cancer Benefit Drug List July 2020. Available at: <http://www.bccancer.bc.ca/systemic-therapy-site/Documents/Policy%20and%20Forms/Benefit%20Drug%20List.pdf> [Last Accessed: 2020/07/29]. 2020;
7. BC Cancer. LYMECHLOR: BC Cancer Protocol Summary for Topical Mechlorethamine in Cutaneous T-cell Lymphoma. Accessed December 16, 2020. http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Lymphoma-Myeloma/LYMECHLOR_Protocol.pdf
8. National Comprehensive Cancer Network (NCCN). NCCN Guidelines for Primary Cutaneous Lymphomas. 2020. [Last Accessed 28 Apr 2020].
9. Trautinger F, Eder J, Assaf C, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome - Update 2017. *Eur J Cancer*. May 2017;77:57-74. doi:10.1016/j.ejca.2017.02.027
10. Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood*. Apr 18 2019;133(16):1703-1714. doi:10.1182/blood-2018-11-881268
11. Gilson D, Whittaker SJ, Child FJ, et al. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Supplementary Information. *Br J Dermatol*. Mar 2019;180(3):496-526. doi:10.1111/bjd.17240
12. CADTH. LEDAGA Clinical Reviewer's Report. 2021.
13. Action. CfDEaRSRfR.Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202317Orig1s000SumR.pdf.
14. European Medicines Agency. Assessment Report. LEDAGA. 2016.:Available at: https://www.ema.europa.eu/en/documents/assessment-report/ledaga-epar-public-assessment-report_en.pdf.
15. *NICE Final appraisal document - Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma 2021*.
16. Canadian Agency for Drugs and Technologies in Health. Procedures for CADTH Reimbursement Reviews. June 2021.