CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

CHLORMETHINE HYDROCHLORIDE (Ledaga)

(Recordati Rare Diseases Canada Inc.)

Indication: For the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients.

January 22, 2021

CADTH

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0242-000
Generic Drug Name (Brand Name)	**Chlormethine Hydrochloride (Ledaga)**
Indication	**For the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients.**
Name of the Clinician Group	**N/A**
Author of the Submission	[redacted]
Contact information	[redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

Lymphoma Canada, a national non-for-profit organization for Canadian lymphoma and CLL patients, coordinated the group clinician response. For more information about Lymphoma Canada, please visit www.lymphoma.ca.

The following clinicians, leading experts in lymphoma across Canada, have provided feedback on this therapeutic for the submitted indication.

Dr. Ivan Litvinov (Lead Clinician)

Dr. Elena Pope

Dr. Kevin Pehr

Dr. Gizelle Popradi

Dr. David Roberge

2. Information Gathering

Please describe how you gathered the information included in the submission.

Clinicians provided responses to the questions in the submission based on research results, clinical experience, and understanding of patient needs and challenges.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Currently, the treatment that can be compared to Ledaga is compounded mechlormethine ointment, which is has limited availability in Canada. The paradigm of treatment for this Mycosis Fungoides (MF) patient population is a prioritization for skin-directed therapies for early-stage (IA-IIA) disease. There is no gold standard treatment and combination therapies have been beneficial (available Alberta and British Columbia treatment guidelines are attached). Mechlormethine is positioned as a key and (first-line in other countries, 2nd line in Canada) therapy for early-stage skin limited disease. Mechlormethine can be compounded into an alcoholic base, although ointment is what is generally used. However, very few pharmacies are capable of compounding it in either base. Furthermore, compounded ointments have limited stability. Additional comparisons include compounded bis-chloroethylnitrosourea (BCNU), which requires regular blood test due to a non-negligible risk of bone marrow suppression/toxicity. Mechlormethine directly results in apoptosis of malignant cells as well as improvement of symptoms of itch/burning caused by MF. Other skin directed therapies for early stage (IA-IIA) MF have variable response rates and include topical steroids (first line treatment), imiquimod (cost not covered for the treatment of MF), tazarotene gel (cost not covered for the treatment of MF), phototherapy (Ultraviolet B, Narrow-Band Ultraviolet B light), photochemotherapy (Psoralen withy Ultraviolet A light), or external electron beam radiotherapy (used for unilesional disease).

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

The addition of effective topical treatment would be extremely useful in the treatment of patients (pivotal clinical trials report clinical response in ~60% of early-stage MF patients using the gel vs. 35-50% using the compounded mechlormethine ointment). The goals of this therapy include disease control, symptom control, and improved quality of life. Importantly, for select skin sites such as scalp and other hair bearing areas, where application of creams and ointments is difficult, having a gel product that can be applied would be very useful in the treatment of these patients. Gel is stable, non greasy, quick drying that ultimately allows for convenient, simple at home administration, thereby encouraging compliance. This would reduce the severity of patient's symptoms, prevent disease progression, improve skin-related quality of life, and improve skin disease scores. Mechlorethamine is a standard and useful treatment, but currently only rarely used because it is not always available and not stable. Further, this option is more convenient than light (phototherapy/photochemotherapy) treatment for patients that live far from a clinic.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Patients who would benefit from this therapy include adult patients with IA-IIA stages of MF with <15% body surface area involvement (Stage IA & IIA <10%; Stage IB >10%) and patients with select skin sites involved by Mycosis Fungoides (e.g., hair bearing areas). Mycosis Fungoides is a chronic disease where patients often experience disease relapse. Hence, most patients throughout the course of their disease cycle through multiple treatments (topical steroids to retinoids to combination of steroids and retinoids, to imiquimod, phototherapy, radiotherapy etc.). Additional effective topical treatment would be extremely useful in the treatment of patients. This is an ideal therapy as it is stable, easy to apply at home (not requiring a clinic visit), has low toxicity, requires no laboratory/blood test monitoring and few side effects. There is a need for formulations that are more convenient to apply since MF is a chronic disease.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

MF is the most common form of cutaneous lymphoma, with most patients in the early stage of disease (stage IA-IIA represents >70% of cases). It is a rare type of skin cancer with limited therapeutic options in early stages. Appropriate treatments for this patient group include skin-directed therapy with mustargen. However, as noted in section 5.1, treatments tend to fail after a while, and patients have to cycle through different treatments. This therapy should be made available to those who have failed or not tolerated at least one prior skin directed therapy (e.g., potent and ultrapotent topical steroids 3 months duration or phototherapy 30 treatments). This therapy will offer more choices for this population, and a stable gel formulation would be of particular benefit to patients with involvement of hairy areas (scalp, bearded area); locations where the existing topical preparations (compounded creams/ointmens) could not be applied.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

This treatment would be ideal for patients with Mycosis Fungoides with <10-15% BSA disease (stages IA-IIA) and with disease affecting hair bearing areas. This would be a second line therapy for patients who have failed topical steroids, but who are neither severe enough, or progress quickly enough, to require systemic therapy. This drug can be used as monotherapy or in combination with other treatments with non-overlapping toxicities (e.g., topical steroids or topical retinoids – i.e., tazarotene gel).

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

As in section 6.1, topical corticosteroids (for 3 months) and NB-UVB (narrow band ultraviolent B) are considered the first line treatments in patients with mild disease. For certain areas such as beard and scalp, there are no good first line alternatives. Therefore, this topical agent can be used as a first line agent in these locations. For other locations, this would be seen as a 2nd line treatment, with the main alternative of UVB. If UVB therapy is not available this agent can be used after potent or ultrapotent topical steroids have failed.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

Topical steroids could be administered again if this therapy fails. This would be within the 2nd line treatment options. There are 3rd and 4th line treatments if 2nd line therapy fails. Frequently multiple therapies are used that have synergistic beneficial effects, but different side effects. Progressive disease would require other treatment modalities (topical tazarotene, imiquimod for limited [<10-15% BSA], radiation, photochemotherapy or systemic therapies with retinoids, methotrexate, extracorporeal photopheresis and/or interferon for more extensive disease). If there is a response and relapse after treatment discontinuation, restarting the therapy with mechlormethine gel and a slower wean would be appropriate. For many patients, greater access to this therapy would displace Ultraviolet B (UVB) and other therapies, except for a short course of potent steroids and radiotherapy (for unilesional disease).

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

This topical treatment will be used as a second line therapy for patients who have failed topical steroids and or phototherapy (or if phototherapy is not available or contraindicated), specifically patients with early-stage (stage IA-IIA) MF. This treatment will especially be considered for patients affected with the disease in hair bearing areas.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

The diagnosis of early MF can be challenging as it is based on clinico-pathological correlation. Ideally patients should be evaluated in a multidisciplinary clinic or by specialized dermatologists with biopsy skin tissue reviewed by a specialized pathologist. Only patients with a pathological confirmation in the early stages of disease (stages IA-IIA) would be offered this therapy. Likely initial skin directed therapy would include topical steroids and /or phototherapy (unless phototherapy is not available or contraindicated – as in porphyria or solar urticaria patients). As such, mechlormethine gel would likely be a 2nd line therapy, it is reasonable to consider that diagnosis would have been already properly established. Progression or lack of response of skin compartment is decided based on clinical exam using mSWAT (modified severity weighted assessment tool) and VAS (visual activity score) as well as DLQI (Dermatology life quality index) and Skindex-29 tool for pruritus assessment. There would not otherwise be any other considerations for selecting patients to receive this treatment.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Patients may be less suited for this therapy if they have thick lesions, erythrodermic patients, and patients with folliculotropic/syringotropic (i.e., deeper seated) disease. Further, MF patients in the advanced stages (>III) or tumor stages (IIB), and pediatric patients (<18 years of age) would be least suitable for treatment with this therapy.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

As in section 6.5, there would not be a consideration for selecting patients and patients would be identified through clinic. There is no predictor of response except the occurrence of contact dermatitis to mechlormethine gel, which is associated with a better clinical response and the thickness of the plaques (thinner lesions exhibit better clinical response).

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Clinical improvement (thinning of the plaques or disappearance at 3-6 months after daily application). Pathological confirmation of response is not required. Outcomes to determine patient response can include mSWAT (modified severity weighted assessment tool) and VAS (visual activity score) as well as DLQI (Dermatology life quality index) and Skindex-29 tool for pruritus assessment.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

The treatment will be used for at least 6 months daily before declaring it as ineffective if no objective response is observed. If skin improvement is noted along with the resolution of the plaques/patches the treatment will be continued for 1 year at which point the patient can be switched to a different therapy or this therapy could be tapered to less frequent usage.

6.10. How often should treatment response be assessed?

Response:

Treatment response should be assessed every 3-6 months for efficacy and safety. It may take >9-12 months to achieve maximum clinical response.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

1. Lack of clinical response (or loss of clinical response if previously responsive).

2. Development of persistent and severe allergy or other prohibitive side effects to continued usage including severe dermatitis (redness, skin breakdown) that interferes with the quality of life and is not responsive to dose decrease and topical steroids. Notably, development of mild transient contact dermatitis at the site of the treated lesion corresponds with improved clinical response of the malignant skin patch/plaque.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

For treatment, it is recommended that patients attend a Multidisciplinary clinic or specialist with interest/expertise in this disease. This would include a hospital-based subspecialty clinic, however any outpatient setting in specialized clinics or community setting is appropriate.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

n/a

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

n/a

8. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   Lymphoma Canada helped to coordinate the group of clinicians for this submission, however they were not involved analyzing or adding feedback to any of the responses in this submission.

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. **Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information

Name	*Dr. Ivan Litvinov*
Position	McGill University Health Centre (Assistant Professor of Dermatology, Director of Research in Dermatology)
Date	*Please add the date form was completed (DD-MM-YYYY) 01-19-2021*
☒	**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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Novartis	☐	☐	☒	☐
Merck	☐	☐	☒	☐
Bristol Myers Squibb	☐	☐	☒	☐
Abbvie	☐	☒	☐	☐
Galderma	☒	☐	☐	☐
Bausch	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
Sun Pharma	☒	☐	☐	☐
Johnson & Johnson	☒	☐	☐	☐
Mallinckrodt	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Kevin Pehr*
Position	*Dermatologist. Chief of McGill Multidisciplinary Cutaneous Lymphoma Clinic.*
Date	*19-12-2020*
☒	**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

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	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. David Roberge*
Position	*Radiation Oncology, Centre hospitalier de l'University de Montreal*
Date	*20-12-2020*

☒	**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

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	☒	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Elena Pope*
Position	*Head, Section of Pediatric Dermatology, The Hospital for Sick Children and Professor, University of Toronto*
Date	*28-12-2020*
☒	**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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Novartis	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐
Boehringer-Ingelheim	☒	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Dr. Gizelle Popradi*
Position	*Assistant Professor, McGill University Health Center*
Date	*01-01-2020*
☒	**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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Novartis	☐	☒	☐	☐
Merck	☒	☐	☐	☐
Seattle Genetics	☒	☐	☐	☐
Jazz Pharma	☒	☐	☐	☐

Kite/Gilead	☒	☐	☐	☐
Abbvie	☒	☐	☐	☐
Servier	☐	☒	☐	☐
Taiho Pharma	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐