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CADTH Reimbursement Recommendation

Chlormethine Gel (Ledaga)

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

Sponsor: Recordati Rare Diseases Canada, Inc.

Final recommendation: Do not reimburse

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Ledaga?

CADTH recommends that Ledaga should not be reimbursed by public drug plans for the 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.

Why Did CADTH Make This Recommendation?

- Although evidence from a clinical trial found that Ledaga was not inferior to chlormethine ointment, chlormethine ointment is not used in Canada. There was no evidence to show whether Ledaga works better than or similar to treatments for MF-CTCL that are currently used in Canada.
- There is an unmet need for treatments with fewer side effects, but it remains unknown whether Ledaga has fewer side effects compared with other treatments for MF-CTCL used in Canada.

Additional Information

What is Mycosis Fungoides-Type Cutaneous T-Cell Lymphoma?

MF-CTCL is a type of blood cancer that starts in the skin with visible patches and plaques which are associated with itchiness, pain, or burning. It is estimated that every year there are 5.6 new cases of MF-CTCL per million persons.

Unmet Needs in Mycosis Fungoides-Type Cutaneous T-Cell Lymphoma

Currently, treatments for MF-CTCL work in most but not all patients, and long-term use may cause side effects. Phototherapy is one of the treatments for MF-CTCL, but it is difficult to access for many patients. Unmet needs for patients with MF-CTCL include treatments that can cure MF-CTCL, are easily accessible, and have fewer side effects.

How Much Does Ledaga Cost?

Treatment with Ledaga is expected to cost approximately $2,995 per month.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that chlormethine gel (160 mcg, 0.02%) should not be reimbursed 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.

Rationale for the Recommendation

pERC could not recommend chlormethine gel be reimbursed because of several important limitations with the reviewed randomized controlled trial (RCT), Study 201 (N = 260), that resulted in a high degree of uncertainty regarding the magnitude of the treatment effect of chlormethine gel. Study 201 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. No comparative data were available between chlormethine gel and the current standards of care for early stage MF-CTCL (i.e., phototherapy, topical retinoids, and topical corticosteroids). Although Study 201 found chlormethine gel was noninferior to chlormethine ointment for relieving skin-related signs and symptoms of MF-CTCL, the comparison was relative to an alternative formulation of the treatment that is no longer used in Canada. It is also unknown whether the degree of change on the primary outcome measure that was used in the RCT (the Composite Assessment of Index Lesion Severity [CAILS]) represents a clinically significant improvement because of the lack of a validated estimate of a minimally important difference for the scale. Patients also expressed a desire for treatments with fewer adverse effects. Chlormethine gel was associated with similar percentages of patients who had serious adverse events (10.9% versus 8.7% with chlormethine ointment) and similar withdrawals due to adverse events (21.9% versus 18.1% with chlormethine ointment), with most events being skin-related. pERC concluded that the overall and long-term balance between the potential benefits and harms of treatment with chlormethine gel are highly uncertain because of the limitations with the clinical evidence.

Discussion Points

- pERC discussed patient input that MF-CTCL negatively affects many aspects of life including employment, daily activities, and relationships. Even in the early stages of the disease, the symptoms (e.g., itching and pain) can have a significant impact on patients' mental, emotional, and physical well-being. Patients reported that they often need to travel to receive treatments for MF-CTCL and even after successful treatment the condition may return necessitating them to cycle between treatments resulting in a considerable impact on their time and quality of life. pERC recognized the need for an effective alternative treatment option that may be more convenient for patients. Given the lack of data on health-related quality of life, pERC concluded that the evidence did not clearly demonstrate that chlormethine gel meets these important patient needs.
- There are no data comparing chlormethine gel with any relevant comparators; thus, pERC could not determine whether chlormethine gel provides superior, similar, or no clinical or economic benefit versus currently available therapies for MF-CTCL.

- The sponsor-submitted pharmacoeconomic model compared chlormethine gel with phototherapy, which was considered an appropriate comparator. However, the efficacy of chlormethine gel relative to phototherapy in the model was based on naive indirect comparisons without adjustment for differences in patient characteristics. Given the lack of robust comparative evidence, CADTH could not derive a base-case estimate of the cost-effectiveness of chlormethine gel compared with phototherapy. When CADTH performed exploratory reanalyses assuming confidence in the naive comparison of chlormethine gel and phototherapy, chlormethine gel had a 0.2% probability of being cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY) in the population of patients enrolled in Study 201.
- pERC discussed the longer-term data from Study 202 (N = 100), an open-label, single-arm extension study of Study 201 that evaluated the efficacy and safety of a higher concentration of chlormethine gel (0.04%) for up to 7 months of treatment, followed by an additional 12 months of observation. pERC could not draw concrete conclusions on the results of Study 202 because of the open-label administration of treatment, use of a strength of chlormethine that is not approved, and absence of a comparator group.

Background

Chlormethine gel (Ledaga) has a Health Canada indication for topical treatment of stage IA and IB MF-CTCL in adult patients who have received prior skin-directed therapy. Chlormethine is a bifunctional alkylating agent that inhibits rapidly proliferating cells. It is available in 60 g tubes containing 160 mcg of chlormethine hydrochloride (equivalent to 0.02% chlormethine) per gram of gel. The gel is applied as a thin film once daily to affected areas of the skin. The product monograph notes that treatment should be stopped for any grade of skin ulceration or blistering, or moderate-to-severe dermatitis (e.g., marked skin redness with edema). Treatment with chlormethine gel can be restarted after the skin-related effects have resolved at a reduced frequency of once every 3 days. If restarted treatment is tolerated for at least 1 week, the frequency of application can be increased to every other day for at least 1 week and then to once-daily application if tolerated.

Sources of Information Used by the Committee

To make their recommendation, pERC considered the following information:

- A review of 1 RCT and 1 open-label extension study
- Patients' perspectives gathered by patient groups from 3 organizations: Lymphoma Canada, Canadian Skin Patient Alliance (CSPA), and Cutaneous Lymphoma Foundation (CLA)
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Two clinical specialists with expertise diagnosing and treating patients with MF-CTCL
- Input from 1 clinician group, coordinated by Lymphoma Canada
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Lymphoma Canada, with the collaboration and input of CSPA and CLF, conducted an online survey of cutaneous lymphoma patients from September 2020 to January 2021. Overall, 233 patients with MF-CTCL responded to the survey, of which 210 (90%) were diagnosed with MF-CTCL. Fifty-six (33%) patient respondents indicated they had experience with chlormethine gel.

Patients reported having visible patches or lesions, itchiness, pain or burning of the skin or lesions, plaques, and rash-like skin redness. The patients indicated that even in the early stages of the disease, these symptoms negatively impact their quality of life and mental and emotional well-being, their self-image, family relationships, intimate relationships, and work.

The patients indicated that having a choice in treatment options was extremely important to them. The patients reported that they want treatments that result in longer survival, better quality of life, longer remission, fewer side effects, and easier or faster treatment application. Among the patients who had experience with chlormethine gel, 74% indicated that they would take it again if it were available to them.

Clinician Input

Input from clinical experts consulted by CADTH

The clinical experts consulted by CADTH noted that current treatments for MF-CTCL have limitations. Unmet needs include treatments that can be curative, easily accessible, and well-tolerated. Topical corticosteroids are not curative, and it is unclear if they can prevent disease progression. Long-term use can cause side effects. Phototherapy may not be accessible to some patients, and it may cause skin atrophy and increased risk of skin cancer. Topical chlormethine causes dermatitis and may not be tolerated, especially when large surface areas are involved. These treatments have efficacy ranging from 60% to 80%, depending on disease severity. Therefore, different treatment options may be required for refractory disease.

The clinical experts anticipated that it is unlikely that chlormethine gel will shift the current treatment paradigm as it is only supplied in 60 g tubes and can only be used for treatment of small surface areas (< 10% body surface area) because of its potential to cause skin irritation. It may be used to treat lesions refractory to topical corticosteroids or when phototherapy is not accessible or is ineffective. The clinical experts identified patients least likely to benefit from chlormethine gel as those with extensive disease (> 20% affected body surface area) or those with tumours.

Clinician group input

A group of 5 clinicians, coordinated by Lymphoma Canada, provided input.

The clinicians noted that the addition of effective topical treatment would be useful in the treatment of patients with MF-CTCL. The goals of this topical therapy include disease control,

symptom control, and improved quality of life. Importantly, for select skin sites such as the scalp and other hair bearing areas, where application of creams and ointments is difficult, having a gel product that can be applied would be especially useful in the treatment of these patients. Gel is stable, non-greasy, and quick drying formulation that allows for convenient, simple at home administration, and may encourage adherence to treatment. Chlormethine is a useful treatment, but currently rarely used because it is not always available. This option is more convenient than light (phototherapy or photochemotherapy) treatment for patients that live far from a clinic. 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, and patients with select skin sites involved by MF-CTCL (e.g., hair bearing areas).

Drug Plan Input

The key question raised by the Provincial Advisory Group (PAG) was whether use of chlormethine ointment as a comparator to chlormethine gel in the pivotal trial was clinically relevant. Chlormethine ointment is not currently funded or available for use as a treatment in most jurisdictions. In terms of place in therapy, patients enrolled in Study 201 were required to have been treated with at least 1 prior skin-directed therapy. PAG asked if this would apply to routine clinical care. Another question concerned the quantity of chlormethine gel dispensed (60 g tube) and the quantity needed to treat skin lesions.

Clinical Evidence

Clinical Trials

Study 201 was a randomized, observer-blinded, controlled, multi-centre trial conducted in 13 academic centres across the US. The objective of the study was to investigate the safety and efficacy of chlormethine 0.02% topical gel for patients with early stage MF-CTCL (May 2006 to August 2011). It was designed as a noninferiority trial comparing chlormethine 0.02% gel with chlormethine 0.02% compounded ointment over a 12-month period. Blocked randomization stratified by MF-CTCL stage (IA versus IB, IIA) was performed. In total, 260 patients with biopsy-confirmed stage I or IIA (cutaneous only) MF-CTCL who had received at least 1 prior skin-directed therapy for MF-CTCL were randomized 1:1 to receive treatment with chlormethine 0.02% gel (n = 130) or chlormethine 0.02% ointment (n = 130). All patients completed a washout period of MF-CTCL therapies for 4 weeks before initiating the trial treatments. Patients in both treatment groups were instructed to apply the treatment once daily to specific lesions, or to the total skin surface depending on the extent of body surface area coverage of the patients. The primary efficacy end point of Study 201 was response rate, defined as a greater than or equal to 50% improvement in patients' CAILS score from baseline to 12 months. A patient was considered a responder if the response was maintained for at least 2 consecutive visits (or at least 28 days). The main secondary efficacy end point was response rate using the Severity-Weighted Assessment Tool (SWAT). Other outcomes were change in total percentage body surface area response rate, time to response, duration of response, time to disease progression, and safety and tolerability.

Most patients were between 18 and 64 years of age and 40.8% were female. Greater than 54% of patients had stage IA disease and 44.2% of patients had stage IB disease at baseline;

2 patients in each treatment group had stage IIA disease at baseline. The most common previously used skin-directed therapy was corticosteroids, used in 86% of patients in both treatment groups.

In the intention-to-treat population, the confirmed response rate based on the CAILS score was higher for chlormethine gel than chlormethine ointment (58.5% versus 47.7%); 13.8% and 11.5% of patients in the chlormethine gel and chlormethine ointment treatment groups, respectively, achieved complete response (i.e., no evidence of disease with a 100% improvement). The ratio of the response rate of gel to ointment was 1.23 (95% confidence interval [CI], 0.97 to 1.55), meeting the pre-specified criterion for noninferiority (≥ 0.75 for lower bound of 95% confidence interval [CI]). The SWAT response was 46.9% for chlormethine gel and 46.2% chlormethine ointment. The ratio of response was 1.02 (95% CI, 0.78 to 1.32). Body surface area response was achieved in 44.6% patients treated with chlormethine gel and 43.1% of patients in the chlormethine ointment group, with a ratio of response of 1.03 (95% CI, 0.78 to 1.36). Time to response in the chlormethine gel group was 26 weeks versus 42 weeks in chlormethine ointment group. Response was maintained in 86% of patients in chlormethine gel group and in 82% of patients on the chlormethine ointment group.

During the trial period, 84.4% of patients treated with chlormethine gel and 90.6% of patients treated with chlormethine ointment experienced at least 1 adverse event. Most adverse events in both treatment groups were skin-related. The frequency of skin irritation was higher in the gel group compared with the ointment arm (25.0% versus 14.2%). Serious adverse events occurred in 10.9% and 8.7% of patients in the chlormethine gel and ointment groups, respectively. Approximately 22% of patients in the chlormethine gel group and 18% in the chlormethine ointment group withdrew prematurely for adverse events. During the 12-month trial period and the additional 12-month follow-up period (in the extension study, Study 202), 20 non-melanoma skin cancers were detected in 11 (4.3%) patients, which included 10 basal cell carcinomas (5 occurring in a treatment area), 9 squamous cell carcinomas (1 in a treatment area), and 1 Merkel cell carcinoma (not in treatment area). Eight of these patients developed non-melanoma skin cancer during treatment; 3 additional patients developed non-melanoma skin cancer during the 1-year follow-up period.

The key limitations of Study 201 included the choice of a comparator (chlormethine ointment) that is not part of the current standard of care in Canada, uncertainty regarding the clinical significance of the results, and absence of health-related quality of life outcomes.

Indirect Evidence

No indirect evidence was submitted.

Other Relevant Evidence

Study 202 was an open-label, single-arm extension study that evaluated the efficacy and safety of a higher concentration of chlormethine gel (0.04%). Patients in Study 201 who had not achieved complete response based on CAILS on either chlormethine gel or chlormethine ointment during Study 201 were eligible to enroll into Study 202. All patients who enrolled into the study received the higher strength of chlormethine gel (0.04%) for up to 7 months, and were followed and evaluated for adverse events and skin cancers during the 7-month study treatment follow-up and for 5 months thereafter. CAILS responses at the end of Study 202, relative to Study 201 baseline showed an overall confirmed response rate of 75.5%, and responses relative to the Study 202 baseline showed a confirmed response rate of 23.5%.

Overall, 72.4% of patients in Study 202 had an adverse event and 6.1% had a serious adverse event. The most common adverse events were skin irritation (11.2%), erythema (10.2%), and pruritus (6.1%). A lack of systemic exposure to chlormethine or its degradation product was confirmed in this study.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with MF-CTCL
Treatment	Chlormethine gel
Submitted drug price	$2,710.38 per 60 g tube ($45 per gram)
Cost per course	Topical treatment, used daily on affected areas. Cost per course varies for each patient.
Comparator	Phototherapy (consisting of PUVA and UVB)
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Lifetime (44 years)
Key data sources	Chlormethine gel informed by Study 201; Phototherapy informed by Phan et al. (2019) and Whittaker et al. (2012)
Submitted results	Chlormethine gel is dominant (less costly [incremental costs: -$19,893] and more effective [incremental QALYs: 0.66]) compared to phototherapy.
Key limitations	• The efficacy of chlormethine gel relative to phototherapy in the model was based on naive unadjusted comparisons. The comparative clinical efficacy of chlormethine gel relative to other treatments, including phototherapy, for MF-CTCL is unknown. The sponsor incorporated data for phototherapy from multiple sources, which introduces considerable uncertainty to comparative effectiveness estimates. • The sponsor's submitted pharmacoeconomic analysis does not adequately reflect the clinical management of MF-CTCL. First, the target population in the sponsor's submission includes patients with early- (stage IA, < 10% skin involvement) and later-stage (stage IIA/IB, stage IIB+; 10% to 80% skin involvement) disease. Clinical experts consulted by CADTH indicated that chlormethine gel would be used in practice only for patients with less than 10% skin involvement. Second, treatment effectiveness is modelled in terms of SWAT score, which does not capture all considerations for clinical decision-making (e.g., patient-reported quality of life improvements). Third, the sponsor assumed that treatment response would be assessed after 13 weeks of phototherapy and 6 months of chlormethine gel treatment; whereas clinical experts indicated that response to both treatments would be assessed after 6 months. • The costs associated with wound care were overestimated. Clinical experts indicated that wound care dressings are rarely required for patients receiving skin-directed therapy and are not typically used in this population.

Component	Description
	• The daily use of chlormethine gel was underestimated. The sponsor incorporated the median daily use of chlormethine gel daily use from Study 201 (1.8 g), which was lower than the mean daily use (2.21 g). The sponsor assumed that patients would use the same amount of chlormethine gel daily regardless of the extent of body surface involvement, which is unlikely. • The efficacy of chlormethine gel in patients with advanced disease is uncertain. The sponsor assumed that the efficacy of chlormethine gel observed in Study 201, which enrolled predominantly patients with stage I disease, would be equivalent in later-stage disease. No data were provided to support this assumption. • Health state utility estimates are uncertain. The utility values applied to each health state incorporated in the model were obtained from a vignette study in which clinicians rated how they believed patients with different levels of disease burden would assess their quality of life, with disease burden measured by SWAT score. The sponsor assumed a linear relationship between SWAT score and health-related quality of life, which has not been validated. Utility mapping introduced additional uncertainty into the analyses.
CADTH reanalysis results	• Given the lack of the comparative clinical evidence, the cost-effectiveness of chlormethine gel is unknown. CADTH undertook exploratory reanalyses to correct the sponsor's model using best available evidence, but the validity and interpretability of the results are limited by the quality of comparative effectiveness evidence. • CADTH's exploratory reanalyses included: using a common source for phototherapy effectiveness estimates, revising the timing of response assessment for phototherapy, excluding costs associated with wound care, and increasing the daily dose of chlormethine gel. CADTH was unable to address the lack of head-to-head comparative clinical data, lack of data to inform chlormethine gel efficacy in late-stage disease, and uncertainty related to health state utility values. Compared with phototherapy, the ICER for chlormethine gel was $358,310 per QALY. However, these analyses should be viewed only as exploratory given the absence of any direct comparative clinical data for chlormethine gel.

ICER = incremental cost-effectiveness ratio; MF-CTCL = mycosis fungoides-type cutaneous T-cell lymphoma; SWAT = Modified Severity-Weighted Assessment Tool; PUVA = psoralen and ultraviolet A; QALY = quality-adjusted life-year; UVB = ultraviolet B; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- The number of patients eligible for chlormethine gel is uncertain.
- The costs related to chlormethine gel and phototherapy are underestimated.

CADTH reanalysis included: updating the prevalence of MF-CTCL, using the proportion of patients eligible for coverage to calculate market size, increasing the daily dose of chlormethine gel, and increasing the duration of phototherapy.

Based on CADTH reanalyses, the budget impact to the public drug plans of introducing chlormethine gel for patients with MF-CTCL is expected to be $2,480,803 in year 1, $8,130,658 in year 2, and $19,702,020 in year 3, for a 3-year total budget impact of $30,313,481. The estimated budget impact is sensitive to the proportion of MF-CTCL patients who are eligible for public drug plan coverage, the daily dose of chlormethine gel, and the price of chlormethine gel.

CADTH

CADTH pan-Canadian Oncology Drug Review Expert Review Committee Information

Members of the Committee

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Initial meeting: June 10, 2021

Regrets: None

Conflicts of interest: None

Reconsideration meeting: November 10, 2021

Regrets: None

Conflicts of interest: None